Non-Invasive Measurement of Trigeminal Nerve Somatosensory Evoked Potentials

by

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Patent Pending

Frontispiece

"Pain is a more terrible lord of mankind

than even death itself"

- Albert Schweitzer, 1953

Dedication

This thesis is dedicated to those individuals
who struggle to live with chronic pain on a daily basis.
Their courage and resilience are inspiring.

This thesis is also dedicated to the family
and friends of those who suffer
for they suffer too.

To all of 'the Energizer bunnies' who keep on
going and going despite the odds.

To the memory of those who have given up
the daily struggle because it was too much to bear.
May they rest in peace.

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Table of Contents

Frontispiece....2

Dedication....3

Acknowledgments....4

Table of Contents....5

List of Tables....8

List of Figures....9

List of Abbreviations....13

Abstract....14

Introduction....15

Terminology....15

The accident....17

The nature of whiplash injury....19

After the accident....20

The sequelae of whiplash....22

The neuropsychological domain....23

Cranial nerve roots and functions....25

The Trigeminal Nerve Complex....26

Trigeminal function....26

Trigeminal neuroanatomy....26

Physiological considerations....28

Trigeminal-Cervical relationship....28

Assessment of trigeminal function....30
Other post-injury sequelae....31
Involvement of the trigeminovascular complex after Injury....31
Temporomandibular joint dysfunction....33
The Connection between the trigeminal complex and TMD....35
Trigeminal brainstem and thalamic physiology....35
The Role of Electrophysiology in Assessment....37
Measurement of somatosensory evoked potentials....37
Review of existing procedural detail....40
Rationale and Hypotheses....47
Hypothesis I - Feasibility of noninvasive electrode use....48
Hypothesis II - Altered TSEP characteristics....48
Methods and Results....49
Apparatus....49
Participants....52
Hookup procedures....53
Issue 1: Stimulus Delivery....55
Discussion - Stimulus Delivery....62
Issue 2: Stimulation Artifact....68
Discussion - Stimulation Artifact....76
Issue 3: Cortical Recording Sites....85
Discussion - Cortical Recording Sites....90

Issue 4: Stimulation Electrode Design and Placement Location.....93

Discussion - Stimulation Electrode Design and Placement Location.....96

Preliminary Participant Results.....101

Trials on Uninjured Participants.....101

Trials on Whiplashed Participants.....102

Discussion - Preliminary Experimental Results.....105

General Discussion.....108

Data Integrity - Artifact and Contamination.....109

Hardware - Present Limitations and Future Improvements.....118

Implications for Future Research.....121

References.....126

Tables.....144

Figures.....152

List of Tables

Table		Page
1	Cranial Nerve Function	145
2	Constant Current DC Stimulator Calibration	149
3	TSEP Waveform Peak Amplitudes	150
4	Results of Peak Amplitude ANOVA	151

List of Figures

Figure Page

1. Overview of the Trigeminal Nerve....153
2. Mandibular Branch of the Trigeminal Nerve....154
3. Anatomical Route of the Trigeminal Nerve to the Somatosensory Cortex....155
4. Diagrammatic Representation of Trigeminal Stimulation and Recording Apparatus....156
5. Amplifier-generated artifact due to amplifier overload....157
6. Reduced artifact through alternating polarity manual trial....158
7. Reduced artifact through alternating stimulus polarity....159
8. Normal 10 mA current pulse on chicken thigh....160
9. Normal 10 mA current pulse on human wrist....161
10. Breakdown of 20 mA current pulse on human wrist....162
11. Single frame representation of EMG movement artifact 163
12. Robust TSEP waveform in top frame and arithmetically-diluted average in bottom frame....164
13. Absence of recorded waveform due to low amplifier gain....165
14. Stimulus artifact with high frequency contamination overlay....166
15. Massive stimulus artifact recorded over a 50 ms epoch....167
16. Reduced stimulus artifact after amplifier gain correction....168

List of Figures (Cont.)

Figure Page

17. Waveform illustrating amplifier ringing and high frequency contamination....169

18. AC-coupled filter generated slow-wave decay artifact....170

19. Heavy RFI noise contamination following bandpass filter removal....171

20. Emerging SEP waveform with lower cortical recording electrode impedances....172

21. Unreproducible waveform - trial 1....173

22. Unreproducible waveform - trial 2....174

23. Waveform illustrative of data corruption due to data drop out....175

24. Emerging TSEP waveforms from separate stimulus pulse recording....176

25. Arithmetic average of separate pulse waveforms in Fig. 24....177

26. TSEP waveform from Cc cortical recording site....178

27. High frequency contamination from poor cortical electrode impedance....179

28. Remaining noise contamination in Fig. 27 after application of nine-point rolling average filter....180

List of Figures (Cont.)

Figure Page

29. Separate pulse trials from erroneously landmarked cortical recording site....181

30. Averaged waveform from erroneously landmarked cortical recording sites in Fig. 29....182

31. Single trial waveform with evident 60 Hz noise contamination....183

32. Waveform contaminated with 60 Hz noise due to poor ground electrode impedance....184

33. Waveform arising from initial lip stimulation trial....185

34. Waveform arising from erroneous lip placement of stimulation electrodes....186

35. TSEPs from bipolar lip stimulation - recorded from Ccl scalp location....187

36. Average of separate polarity stimulation waveforms in Figure 35....188

37. TSEP from mandibular stimulation at 12 mA stimulus intensity....189

38. TSEPs from mandibular stimulation of uninjured participants....190

39. TSEPs from mandibular stimulation of whiplashed participants....191

List of Figures (Cont.)

Figure Page

40. Superimposed averaged uninjured and averaged whiplashed TSEPs.....192

41. TSEP from whiplashed participant - 50 µs stimulus pulse width and 100 µs stimulus pulse width.....193

List of Abbreviations

A2D - analog-to-digital

AC - alternating current

CAD - cervical acceleration-deceleration

CNS - central nervous system

DAI - diffuse axonal injury

DC - direct current

DSP - digital signal processor

EEG - electroencephalography

EP - Evoked Potential

ERP - Event Related Potential

ISA - Industry Standard Architecture (PC expansion bus card slot type)

MVA - motor vehicle accident

RFI - radio frequency interference

SEP - somatosensory evoked potential

TSEP - trigeminal somatosensory evoked potential

Abstract

Whiplash injuries are common yet enigmatic to substantiate clinically. Trigeminal somatosensory evoked potentials (TSEPs) were posited as an indicator of trigeminal nerve conduction damage resulting from whiplash. Alternating polarity square-wave current stimuli were applied transcutaneously in the facial region. 379 recorded pilot trials from 27 participants (8 male and 19 female) were utilized to develop a non-invasive recording capability for TSEPs. Stimulus intensity and artifact, cortical recording sites, stimulation electrode design and placement were explored. Statistically significant differences in amplitude of TSEP waveform components at 13, 19 and 27 ms between uninjured and whiplashed participants were noted. Increased stimulus intensity in whiplashed participants was observed to increase TSEP amplitude. The present methodology and hardware are discussed and directions for future advancement of the current process are outlined.

Introduction

In the United States over 50 million trauma-related injuries occur each year (Turk & Melzack, 1992). Of these, there are two million head injuries resulting from motor vehicular accidents alone (Varney & Sheperd, 1991) followed by motorcycle, bicycle, pedestrian or fall from height-type accidents (Netter, 1986; Bigler, 1995). These often result in a broad spectrum of injury to the central nervous system (CNS) with said spectrum encompassing acceleration-deceleration injuries (commonly known as "whiplash"), concussions, contusions, coup-contrecoup injuries, edema, herniation, and hemorrhage. The mechanisms of physical injury may be represented as a continuum in which the degree of biological damage and functional disturbance increases as the severity of the accidental forces increase (Dixon, Taft, & Hayes, 1993). The present thesis explores technical aspects of trigeminal somatosensory evoked potentials as a possible means for detecting subtle brainstem level trigeminal nerve injury. The question of whether such a subtle injury could be detectable by the present non-invasive method in cases of whiplash injury is also addressed.

Terminology

Whiplash has long been associated with flexion-extension injuries of the cervical spine which occur in response to rear-impact collisions, most often involving motor vehicles (Gay & Abbott, 1953). An important distinction to be noted would be that the head and neck, while responding to the inertial forces acting on them in the accident, do not physically strike anything inside the

vehicle (Barnsley, Lord, & Bogduk, 1998) in order to be identified as a whiplash injury. Should the occupant's head strike an object within the vehicle, such as the steering wheel, windshield, door post, or even the seat back, those injuries would be differentiated as concussion injuries, rather than whiplash (Foreman, 1995).

The whiplash phenomenon arguably encompasses three components: the whiplash event, as the bio-mechanical reaction suffered by the occupants of a vehicle while being struck by another vehicle; the whiplash injury, as the biological injury or impairment that ostensibly results from the physical forces of the whiplash event; and the whiplash syndrome, as the constellation of symptoms which are attributed to the whiplash injury (Barnsley, Lord,& Bogduk, 1994). To further compound the nomenclature, the use of the term 'whiplash' is often associated with malingering and nuisance insurance claims (Foreman, 1995; Swartzman, Teasell, Shapiro, & McDermid, 1996). In an attempt to move away from the negative connotation of whiplash injuries, the medical term of "cervical acceleration-deceleration syndrome" (CAD) has also been proposed (Croft, 1995, p. 3).

Regardless of the term used to describe it, roughly 10%-15% of whiplashed individuals continue to exhibit chronic symptomology after the usual healing period for musculo-ligamentous injuries (Foreman, 1995; Barnsley, Lord, & Bogduk, 1998). In those cases, there may have been a more substantial degree of injury sustained than previously thought possible, or the degree of injury present could not be accurately detected through normally

utilized diagnostic procedures (Croft, 1995).

The accident

The conventional notion for whiplash injury has been that the cervical spine undergoes forced flexion and subsequent hyperextension as the head reacts to the force of a rear impact (Foreman & Croft, 1995). It had long been believed that there may be some muscular stretching associated with the flexion-extension, but there should be no permanent effects so long as there had been no gross tissue damage (Swerdlow, 1999) or if the head or neck had not physically struck an object inside the vehicle (Foreman, 1995).

In light of recent findings (Croft, 1995; Barnsley, Lord, & Bogduk, 1998) the conventional notion of whiplash biomechanics needed to be reexamined. Recent cadaver and high-speed radiographic experiments demonstrated that,

> "upon impact, the lower cervical spine is thrust upwards and forwards. In the moments after impact, the cervical spine is compressed from below and the lower cervical vertebrae are extended while the upper vertebrae are not. As a result, the cervical spine assumes an S shape during the first 50-75 ms after impact. All segments are progressively extended until the head is thrown backwards into extension." (Barnsley, Lord, & Bogduk, 1998, pp. 210-211).

From these studies, it was observed that the cervical spine experiences physical forces greater than previously thought possible. By mapping the motion vector of the neck through high-speed radiography, it has been seen that the neck experiences accelerations ranging from 0.3 to 3.5 times the force of gravity. The direction of the force changes progressively over time from upwards, to upwards and forward, downwards and forwards, backwards, and finally backwards and upwards (Matsushita et al, 1994; Barnsley, Lord, &

Bogduk, 1998). It is important to note that at the low impacts involved, i.e. speeds less than 5 km/hr, none of the subjects experienced degree of motion beyond the normal range of cervical motion (Matsushita et al, 1994; Barnsley, Lord, & Bogduk, 1998) during the time epoch during which cervical compression was evident.

Matsushita et al (1994) highlight several often overlooked considerations. Variation in individual head size would be seldom accounted for, although it may have a significant effect upon the magnitude of the forces generated (Matsushita et al, 1994). The relative position of the individual within the vehicle seat is often ignored. In cases where an individual was leaning forward, or had a stooped shoulder posture, the upper torso would have been away from the seat back surface. A rear-end impact produces an extension of the thoracic spine, resulting in an upward axial acceleration of the cervical spine, in turn producing a compressive loading of the cervical spine (Croft, 1995; Barnsley, Lord, & Bogduk, 1998). The normal cervical and thoracic spine curvatures would be dramatically affected by these movements, in that the end point of cervical flexion would occur prior to extension (Matsushita et al, 1994). The newer experimental evidence serves to dramatically challenge the conventional notion of whiplash injury.

Studies have also indicated that if the cervical spine were in slight rotation, instead of being in perfect alignment within the sagittal plane, a rear-end impact would force the head further into rotation before extension occurs (Dvorak, Panjabi, Gerber & Wichmann, 1987). Interestingly, Radanov,

Sturzenegger, and DiStefano (1995) reported that individuals, whose cervical spines were in rotation just prior to impact, reported more extensive and persistent physical complaints following the whiplash episode. The experimental evidence is beginning to bear out the importance of the relative position of an individual's cervical spine, in terms of posture as well as extent of side rotation, with respect to the nature of the recalcitrant physical symptomology.

The nature of whiplash injury

Maxwell, Povlishock and Graham (1997) posited that clear neuropathological evidence exists which would suggest that the predominant pattern of injury in cerebral trauma cases would be of a diffuse, non-specific nature. Neuronal shear-strain injuries are such common effects of trauma. The shearing action arises from the rapid acceleration-deceleration forces present during impact, the most common of which would be a flexion-extension type of injury arising from motor vehicular accidents (Goldman, 1991).

An important consideration in whiplash dynamics involves the passive movement of the neck during collision. The cervical musculature, which normally control both the direction and amplitude of neck movement, do not have sufficient time to respond to the virtually instantaneous aspect of the impact (Croft, 1995; Foreman, 1995). The cervical structures then dissipate the collision forces through shear and torque action. The magnitude of the shearing forces could easily exceed the known tolerances of the bony and ligamentous structures leading to damage of these structures within the

cervical spine, even in the absence of an overt head injury (Barnsley, Lord & Bogduk, 1998).

The resulting cervical strain would be made manifest through the stretching or tearing of neuronal fibres which connect neurons with one another and different brain regions. Advances in the study and understanding of diffuse axonal injury (DAI) have revealed changes to the axonal cytoskeleton after injury which have not only structural but important functional consequences (Dixon, Taft, & Hayes, 1993; Maxwell, Povlishock, & Graham, 1997). The generalized damage arises as a result of torn axonal fibres, damage to the supportive glial cell structural network, and degeneration of damaged neuronal fibres (Bigler, 1995; Maxwell, Povlishock, & Graham, 1997). The damage may be widely distributed but most often occurs in deep white matter areas and in the brain stem (Bigler, 1995). The latter observation would be of notable interest given the known anatomical fact that most of the trigeminal subnuclei are located within the brainstem (Wilson-Pauwels, Akesson & Stewart, 1988; Dodd & Kelly, 1991).

<u>After the accident</u>

Given the physical characteristics of the human skull, the path of motion of the head, and the magnitude of impact forces during an accident, the central nervous system could be subjected to significant levels of shearing, twisting, or compression forces (Croft, 1995). The sequelae of these physical forces may be manifested in damage to numerous cervical structures including the muscles, ligaments, vascular structures, bony intervertebral discs, and cranial

nerve roots (Olsnes, 1989; Croft, 1995). As part of the assessment of accidental injury, diagnostic imaging comprised of magnetic resonance imaging (MRI), computerized-axial tomography (CAT) scanning, or radio-nucleotide imaging have been typically employed. Although imaging techniques, as outlined above, can aid in the documentation of the degree of gross physical injury, the functional effects of those injuries often need to be documented through alternative testing protocols due to the inability of imaging techniques to detect the subtle minutiae of neuronal injury.

Such subtle injury may indeed be difficult to detect. Unterharnscheidt (1986) noted that, although light microscopic examination of tissue from animals subjected to whiplash injury failed to reveal any significant lesions, electron microscopic studies of those tissues demonstrated shrinkage of the axoplasm and disruption of myelin lamellae in the upper cervical cord. The rhesus monkeys used for those studies had experienced the application of axial forces to the vertebral column, with the force being of such magnitude that afferent or efferent evoked potential magnitudes were reduced by 50% (Unterharnscheidt, 1986; Croft, 1995).

Electrophysiological evaluation through electroencephalography (EEG) or evoked potentials (EP) has been demonstrated to be useful in the assessment of the extent of significant neural injury or in the localization of areas of traumatic injury (Tippin & Yamada, 1996). EEG and EP evaluation have been helpful in the establishment of neurological recovery prognosis (Tippin & Yamada, 1996). Short latency EPs are considered stable and reliable as they

are less susceptible to the effects of sedatives or the individual's level of consciousness (Tippin & Yamada, 1996). The use of EEG has however been deemed as not useful in the diagnosis of headache or in the investigation of structural damage if other imaging techniques are available (Quality Standards Subcommittee of the American Academy of Neurology, 1995).

The sequelae of whiplash

Following a whiplash injury, commonly reported symptoms often include complaint of headache, pain in the cervical region, visual disturbances, dizziness, tinnitus, arm and chest pain, low back pain, irritability, concentration problems and poor memory (Olsnes, 1989; Teasell & Shapiro, 1998). When these symptoms are compared to the predominant complaints that are known to follow mild head injury, (including physical symptoms such as headache and dizziness, psychological symptoms such as irritability and personality change, and cognitive symptoms including problems with concentration, memory, speed of information processing, and divided attention tasks; Swanson, 1997), one begins to consider a possible relationship between two previously distinct types of injuries. However, one does not need to postulate the existence of a traumatic brain injury to account for the persisting cognitive problems in chronic whiplash patients (Shapiro, Teasell, & Steenhuis, 1993). Although the extensive ongoing debate as to the diagnostic criteria for head injury versus DAI from whiplash would be beyond the scope of the present thesis, the striking similarity between the symptom clusters are nonetheless intriguing.

The neuropsychological domain

In the context of whiplash injuries, it has been argued that the brain could experience concussive effects as a result of the rapid acceleration-deceleration forces which the head and neck are subjected to during a collision (Foreman & Croft, 1995). Several studies have examined the cognitive deficits reported by individuals after a whiplash injury, albeit in the absence of direct physical impact within the car, with inconclusive results as to ongoing sequelae and the reasons thereof (Hugenholtz, Stuss, Stethem & Richard, 1988; Radanov, DiStefano, Schnidrig, Sturzenegger, & Augustiny, 1993).

Numerous studies have documented the presence of ongoing symptomatology in patients who have not experienced a loss of consciousness (Olsnes, 1989; Ettlin et al, 1992; Klein, Houx, & Jolles, 1996) or who have not struck their head on any object during the impact (Croft, 1995). There are, however, others that argue that a loss of consciousness and post-traumatic amnesia are necessary before one could consider the possibility that a neural insult or even a head injury had occurred (Asarnow, Satz, Light, Lewis, & Neumann, 1991). Even the diagnostic criteria for headache highlight the distinction: postconcussive headache requires a period of unconsciousness at the time of trauma; postcontusion headache requires radiographic evidence of brain contusion; post-whiplash headache requires only onset at or after the time of suspected whiplash trauma (Evans, 1992; Barcello & Rizzo, 1996). The debate continues as to whether or not the physical movement of the brain within the skull during CAD would be sufficient to create focal lesions of the

neural tissue (Dieter, 1999).

Neuropsychological assessments tend to focus on the gross deficits of mental abilities and are often insensitive to subtle alterations in central nervous system function which might, nonetheless, have serious consequences for long term recovery and adaptation. Functional alterations after injury may include both overt changes in behaviour or ability, which tend to be noticed by family members and tend to be detectable by the typically performed clinical assessments, but also subtle or covert changes, which may be undetected in the clinical setting or in the absence of secondary challenges such as daily stresses (Dixon, Taft, & Hayes, 1993; Cicerone, 1996). Consideration is rarely given to non-cortical neural damage, nor do such assessments fully evaluate the existence of chronic pain and the sequelae thereof.

In an attempt to elucidate the sequelae of neural insult, investigators have explored the functional deficits that remain following the injury. Three symptom clusters have been documented following post-concussive syndrome. These symptoms generally fall into three broad categories: cognitive (e.g., memory impairment, concentration and attention difficulties); emotional/psychosocial (e.g., mood changes, depression, irritability and apathy) and psychophysiological (e.g., insomnia, fatigue, headache, dizziness, and blurred vision) (Binder, 1986; Rizzo & Tranel, 1996). The challenge facing the diagnostician would be the differentiation between whiplash versus postconcussive injury given their similar clinical presentation. The diagnostic process would also be confounded by the similiar prevalence of the primary

presenting complaints in other medical or psychological conditions as well as in the population in general (Rizzo & Tranel, 1996).

Often, the injured party is left to accept the fact that professionals are unable to fully account for, nor treat, the elusive effects of whiplash sequelae. The goal of this study will be an exploration of the feasibility of utilizing sensory transmission through one of the cranial nerves, namely the trigeminal nerve, as an indicator of injury which would typically go undetected by standard imaging or assessment procedures.

Cranial nerve roots and functions

Injuries involving the cervical column involve numerous anatomical structures which may be damaged during the trauma. The diffuse nature of symptomatic complaints would not be overly surprising given the number of cranial nerves involved in the transmission of sensory and motor signals and whose nerve roots exit the central nervous system at various levels within the cervical spine. Table 1 provides a summary of the cranial nerves and their respective primary functions.

Insert Table 1 about here

Of the 12 cranial nerves, four have some responsibility for the transmission of facial sensory information: the trigeminal, the facial, the glossopharyngeal, and the vagus. Of these four, the trigeminal nerve is responsible for the transmission of significant amounts of facial sensory information without exhibiting any concurrent clinical signs of obvious

dysfunction. In contrast, the other cranial nerves would exhibit obvious signs of impairment, such as Bell's Palsy when dealing with lesions in the facial nerve (Wilson-Pauwles, Akesson & Stewart, 1988). Clinical findings linking the trigeminal nerve to a variety of clinical conditions (Allen & Pronych, 1997) make it an interesting candidate for evaluation of neural dysfunction. In combination with its anatomical properties, the trigeminal nerve became the focus of great interest in the present thesis given its anatomically-mediated propensity to injury in whiplash.

The Trigeminal Nerve Complex

Trigeminal function

As mentioned previously, the trigeminal, or fifth (V) cranial nerve, is primarily involved in the relay of somatosensory afferent information from the face and mouth regions. The trigeminal nerve is responsible for the transmission of sensations of touch, temperature, and pain in the forehead, cheeks, upper jaw and lower jaw (Swerdlow, 1999). In the face, three branches of the trigeminal nerve bilaterally innervate the face: the ophthalmic branch, or V1, innervates the forehead; the maxillary branch, or V2, innervates the cheeks, and the mandibular branch, or V3, innervates the lower jaw. Refer to Figure 1 for an overview of facial innervation by the trigeminal nerve.

Insert Figure 1 about here

Trigeminal neuroanatomy

Figure 2 illustrates in greater detail the spatial configuration of the

mandibular branch, or V3, of the trigeminal nerve. Special note is made of the mandibular branch of the trigeminal traversing the mandible through the mental foramen.

Insert Figure 2 about here

En route from the face to the brain stem, the trigeminal nerve can be divided into the trigeminal main sensory nucleus and the trigeminal spinal tract nucleus, which in turn is comprised of 3 descending subnuclei, the subnucleus oralis, the subnucleus interpolaris, and the subnucleus caudalis. Figure 3 illustrates the trigeminal pathways en route from the face to the somatosensory cortex of the brain. Special note is made of the corresponding anatomical level in the brainstem and spinal cord of the trigeminal subnuclei.

Insert Figure 3 about here

The trigeminal main sensory nucleus is involved primarily with the relay of neural information related to the spatiotemporal properties of discrete oral-facial tactile stimuli, while the trigeminal spinal tract, especially the subnucleus caudalis, is intimately involved in oral-facial nociceptive (pain) and thermoreceptive (temperature) transmission to higher levels of the central nervous system (Hu, Dostrovsky, & Sessle, 1981; Sessle, Hu, Dubner, & Lucier, 1981; Sessle, Hu, Amano, & Zhong, 1986; Sessle, 1987; Hu, Sessle, Raboisson, Dallel & Woda, 1992; Sessle, 1997). Earlier experimental work suggested that facial nociceptive afferents project only to the trigeminal nucleus

caudalis and not to the trigeminal nucleus oralis (Henry, Sessle, Lucier & Hu, 1980). In view of the close structural and functional relationships between the trigeminal and adjacent spinal regions, it had been proposed that the trigeminal subnucleus caudalis and its adjacent reticular formation be referred to as the medullary dorsal horn (Dubner & Bennett, 1983), an important anatomical consideration in current theories of pain propagation (Craig, 1999).

Physiological considerations

Several functional aspects of the trigeminal nerve are also of interest. It has been noted that trigeminal pain pathways differ in a number of respects from spinal pathways: (1) the highest density of receptors which are activated by noxious stimuli are located around the mouth and nose; (2) the ratio of myelinated to unmyelinated nerve fibres is uniquely higher in the trigeminal nerve than in the spinal nerves; and (3) the peripheral conduction distances from the oral-facial area are much shorter than from other densely innervated regions, such as the distal extremities (Dubner, Sessle, & Storey, 1978). The trigeminal system contains both finely myelinated A-delta (A-δ) and unmyelinated C-fibres, and utilizes both for the conduction of nociceptive afferents (Dubner & Bennett, 1983). Trigeminal function includes the transmission of both acute pain through the A-delta fibres and chronic pain through the C-fibres (Melzack & Wall, 1988).

Trigeminal-Cervical relationship

The trigeminal nerve complex, apart from being an essential conduit for sensory messages, also shares some interesting anatomical locales. The

most caudal aspect of the subnucleus caudalis extends into the cervical spinal cord and merges with the spinal dorsal horn at the C1-C2 level (Sessle, 1987). In cervical injuries, the C1-C2 and C5-C6 levels are the most commonly affected levels within the cervical spine (Netter, 1986; Dubuisson, 1994; Foreman & Croft, 1995; Rogers, Joshi, & Dreyfuss, 1998). Nerve root dysfunction at the C1-C2 and C5-C6 levels are also common sequelae of cervical injury (Goldman, 1991; Dubuisson, 1994; Foreman & Croft, 1995). Specifically, the anterior rami of the C1-C4 cervical roots form the cervical plexus which provides motor innervation to the neck muscles and skin innervation for the face, neck, and ear (Rogers, Joshi, & Dreyfuss, 1998). The C5-T1 anterior rami form the brachial plexus which provides the sensory and motor innervation to the shoulder girdle and upper extremities (Rogers, Joshi, & Dreyfuss, 1998). The cervical and brachial plexuses are intimately involved in myofascial pain syndromes and the sequelae of forward head posture (Travell & Simons, 1983). Previous investigations have laid the theoretical groundwork as Rowland (1991) noted that lateral lesions within the medulla and pons of the brain stem generally involve the spinothalamic tract, descending autonomic fibres, the descending sensory tract of the trigeminal nerve, vestibular nuclei, and cerebellar connections. Rowland (1991) generalized that abnormalities in the function of specific cranial nerves help to localize a lesion to a particular horizontal level within the brain stem. It is these properties of the trigeminal nerve which have led to the current proposal for electrophysiological examination in the aftermath of motor vehicle accidents.

Assessment of trigeminal function

At present, there exists no definitive or quantifiable assessment of trigeminal function. Gross sensory evaluation of the trigeminal is performed by means of either a standard wheel-prick test or stroking with a cotton swab (Rothstein, Roy & Wolf, 1991; Okeson, 1995) along areas of the face innervated by the trigeminal nerve. Two additional measures utilized are the corneal reflex and 'jaw-jerk' reflex tests. In the oculomotor 'eye-puff' test, a burst of air is directed towards the cornea of an open eye (Wilson-Pauwels, Akesson, & Stewart, 1988). If the eyelid reflexively closes upon exposure to the air puff, the ophthalmic branch of the trigeminal is considered to be intact (Rothstein, Roy & Wolf, 1991). Alternatively, the cornea could be gently touched with the tip of a cotton swab or a tissue (Okeson, 1995) to elicit the same corneal reflex. The jaw-jerk reflex is mediated via the motor fibres within the mandibular branch of the trigeminal (Dodd & Kelly, 1991). When the mandible is tapped, similar to a knee reflex test, inferior to the chin, the masseter muscle is activated, thus closing the mandible. The jaw-jerk reflex, either being present or absent (Rothstein, Roy & Wolf, 1991; Okeson, 1995), only differentiates gross pathology. Presently, there is a marked absence of any quantifiable measure of trigeminal function in clinical use. The possibility thus exists that minor trigeminal nerve sensory deficits might remain undetectable given the absence of any refined testing techniques for trigeminal function.

Other Post-Injury Sequelae

Involvement of the trigeminovascular complex after injury

Involvement of the trigeminovascular system has also been implicated in the pathogenesis of migraine (Goadsby, 1995). Experimental findings have revealed that, surrounding the large cerebral blood vessels, pial vessels, the large venous sinuses and the dura mater, is a plexus of largely unmyelinated nerve fibres which arise from the trigeminal ganglion and in the posterior fossa from the upper cervical dorsal roots (Goadsby, 1995). Tracing studies have shown that the fibres which innervate cerebral blood vessels arise from within the trigeminal ganglion (Dodd & Kelly, 1991; Goadsby, 1995). Findings have shown that the cell bodies in the trigeminal ganglion, which innervate the large cerebral arteries and dura mater, are bipolar neurons and arise mainly from the ophthalmic branch of the trigeminal nerve (Dodd & Kelly, 1991; Goadsby, 1995). An understanding of the role of trigeminal neural input as having a direct role in the regulation of arterial tone within the head is beginning to emerge (Allen, Barbrick, & Esser, 1995). Research has also demonstrated the convergence of somatovisceral afferents upon nucleus caudalis neurons and their subsequent role in the pathogenesis of migraine through long-term potentiation of nociceptive activation (Okeson, 1991). Since dysregulation of arterial tone has long been thought to be a primary etiology for migraine headaches (Goadsby, 1995), trigeminal involvement is beginning to clearly emerge at the level of neuronal function as well.

Experimental evidence has revealed that the nerves which innervate the

cerebral vessels through the trigeminovascular system contain, almost exclusively, vasodilator transmitters such as calcitonin-related peptide (CGRP) and substance P (Goadsby, 1995). Substance P is noteworthy for its role in the initiation and transmission of pain impulses (Melzack & Wall, 1988). Electrical stimulation of the trigeminal ganglion in both human and feline (Amano, Hu & Sessle, 1986) subjects lead to an increase in extracerebral blood flow and localized release of both CGRP and substance P (Goadsby, 1995). Substance P release enhances excitability by triggering mechanisms which result in long-term, activity-dependent changes in the levels of neuronal excitability, synaptic connectivity, strengthening and plasticity (Meller & Gebhart, 1993). Such changes in turn lead to dorsal horn hyperexcitability and then to excessive depolarization and neuronal excitotoxicity (Dubner & Ruda, 1992). The hyperexcitability due to substance P release is noteworthy given earlier experimental findings that substance P and endogenous opioids play a role in transmission in nociceptive pathways within the trigeminal subnucleus caudalis, the level of the trigeminal complex situated at the C1-C2 level of the cervical spine. The relationship is further pronounced given that alterations or deficits in neuronal transmission may result from a loss of integrity within axonal pathways due to diffuse deafferentation (Dixon, Taft, & Hayes, 1993). Combined with the prevalence of post-traumatic migraine following whiplash injuries (Swerdlow, 1999), dysregulation of the trigeminal nerve complex due to shear injury at the brainstem level emerges as a likely possibility in the etiology of post-traumatic migraine.

Temporomandibular joint dysfunction

Another commonly occurring sequelae of acceleration-deceleration types of injury present clinically under the umbrella of Temporomandibular Joint Dysfunction (TMD) cases (Curl, 1995). TMD encompasses injuries to the temporomandibular joint, the joint capsule, the supporting ligaments, vascular and nervous tissues, and the muscles of mastication (Assael, 1991; Pertes & Gross, 1995). The pain, which can be debilitating, can involve the jaw, head, and neck regions (Curl, 1995; Yu, Sessle, Vernon, & Hu, 1995; Swerdlow, 1999). There is often a concurrent limitation in function since the normal functions of speech and deglutition can be severely compromised (Assael, 1991). TMD cases encompass the clinical spectrum from muscle pain through more complicated internal derangement of the joint structures to the destruction of the bony structures of the jaw and face (Pertes & Gross, 1995). Intimately associated with TMD is the cranial nerve innervation of the face and the muscles of mastication (Assael, 1991). The etiology becomes more intriguing given that the trigeminal nerve is the cranial nerve responsible for the innervation of the muscles of mastication.

A number of studies have pointed to differences between idiopathic TMD cases (those cases which seem to arise spontaneously) when compared to traumatic TMD cases (those cases which are related to an acceleration/deceleration injury, most typically involving a motor vehicle accident (MVA). Kolbinson, Epstein and Burgess (1996) point out that cervical whiplash cases, generally dominated by head, neck, and upper thoracic pain,

are often associated with a variety of poorly explained symptoms including dizziness, vertigo, tinnitus, and blurred vision. Gimse, Bjorgen, Tjell, Tyssedal and Bo (1997) have noted significant differences in learning, memory, prolonged divided attention, concentration, as well as the ability to perform a smooth pursuit neck torsion test, in a whiplashed group compared to a closely matched control group. Kolbinson, Epstein and Burgess (1996) note other symptoms which have been associated with whiplash injuries include arm pain, paresthesias, weakness, dysphagia (difficulty in the ability to swallow), lower back pain, TMD, concentration and memory disturbances, psychologic symptoms and drug dependence (Hohl, 1990; Kolbinson, Epstein & Burgess, 1996).

A further distinction between traumatic versus idiopathic TMD cases emerged. A review of the literature by Kolbinson, Epstein, Senthilselvan and Burgess (1997) revealed that trauma-associated TMD cases have a longer course of problems, have a greater breadth of complaints, have greater pain and dysfunction, have a greater utilization of health-care services and have a poorer treatment outcome than do non-traumatic cases of TMD. Research by Goldberg et al (1996) demonstrated that differences between idiopathic and traumatic cases of TMD were also detectable on neuropsychological testing. Significant differences were noted between the two subject groups on simple and complex reaction-time tasks, Consonant Trigram Test scores, and in immediate recall on the California Verbal Learning Test.

The connection between the trigeminal complex and TMD

The involvement of the trigeminal system in orofacial pain and temporomandibular disorders (TMD) is well documented by clinical evidence (Laskin & Greene, 1992). It was further substantiated by experimental findings demonstrating that the central terminals of major craniofacial muscle afferents, such as those in the masseter and anterior digastric nerves, are mainly distributed in the posterior two-thirds of the subnucleus caudalis and the upper cervical dorsal horn (Hu et al, 1997). Recent research has revealed that a unique feature of many trigeminal nociceptive neurons was their receipt of sensory inputs from nerves supplying widespread sites in the face, mouth, and neck regions. It has been posited that the excitation of these neurons by several convergent afferent inputs could help to explain the referral of pain in headache, toothache, and myofascial pain syndromes (Sessle, 1997; Hu et al, 1997). This serves to strengthen the earlier notion that the trigeminal subnucleus caudalis was involved as a critical relay in jaw nociceptive reflexes and in the ascending pathways which transmit nociceptive information from deep craniofacial tissues to higher brain stem structures (Hu et al, 1997).

Trigeminal brainstem and thalamic physiology

Findings outlining that the primary trigeminal fibres descending in the spinal trigeminal tract are somatotopically organized were noteworthy. Dodd and Kelly (1991) pointed out that sensory fibres from the ophthalmic division of the trigeminal nerve were situated ventrolaterally in the spinal trigeminal tract, while fibres from the mandibular division were situated dorsomedially; the

fibres from the maxillary division were situated in between the ophthalmic and mandibular fibres.

The second-order neurons in the trigeminal pathway lie in the most caudal aspect of the trigeminal nucleus caudalis and in the dorsal horn of the upper cervical spinal cord at the C1-C2 level. The subnucleus caudalis was contiguous rostrally with the principle nucleus which extended caudally through the medulla into the spinal cord up to the C2 level (Dodd & Kelly, 1991). These neurons projected via the quintothalamic tract, which then subdivided prior to its synaptic connections onto third-order neurons in the ventral posteromedial thalamus and the medial nucleus of the posterior complex of the thalamus (Dodd & Kelly, 1991; Goadsby, 1995). The ventral posterior nucleus in turn projected via the posterior limb of the internal capsule to the lateral region of the postcentral gyrus where there is a complete representation of the contralateral face and bilateral representation of the perioral region. The representation of the perioral region is disproportionately large in humans, reflecting the important role of sensory information from the face in its effects on human behaviour (Dodd & Kelly, 1991).

Lesions of the subnucleus caudalis do not completely eliminate all reflexive or behavioral responses to noxious orofacial stimuli whereas more rostral lesions may interfere with pain behaviour evoked by noxious stimuli applied to intraoral or perioral tissues (Sessle, 1997). In addition, the rostral regions have been seen to project to some of the same thalamic regions which are the projection sites of caudalis neurons implicated in pain transmission or

its control (Sessle, 1997).

Since it is generally accepted that nociceptive inputs from the head and oral cavity terminate in the spinal trigeminal nucleus (Dubner & Bennett, 1983), it may be possible that damage to the trigeminal pathway would be evident through an alteration of the conduction capability en route to the thalamus and higher brain centres. The lack of assessment procedures for trigeminal function, other than for gross motor responses through the jaw-jerk or oculomotor reflexes (Wilson-Pauwels, Akesson, & Stewart, 1988; Rothstein, Roy, & Wolf, 1991) complicate the situation even further. The challenge would then exist for a non-invasive process with which to quantify the degree of neural impairment were it to exist.

The Role of Electrophysiology in Assessment

As noted earlier, the use of electrophysiological techniques has been demonstrated as being helpful in the evaluation of neural injury. EEG and EP studies have been used to investigate the degree of neural injury following trauma. Auditory EPs and visual EPs have also been used to test the integrity of the underlying neural systems (Tippin & Yamada, 1996).

Measurement of somatosensory evoked potentials

Dong, Kawakami, and Chudler (1987) posited that the non-invasive measure of evoked potentials were potentially useful in the assessment of the degree, extent and duration of peripheral or central neural injury. The authors demonstrated changes in trigeminal evoked potentials, noting that specific sets of response components were affected depending upon the level of injury

in the trigeminal lemniscal system. A similar paradigm was demonstrated by Synek (1986) as being useful in the diagnosis of lesions of the supraclavicular brachial plexus (a network of lower cervical and upper dorsal spinal nerves which supply the arm, forearm, and hand). Abnormal median nerve somatosensory evoked potentials have also been noted in multiple trunk lesions and multiple root tears (Synek, 1986). Chiappa and Hill (1997) noted some 29 studies involving altered somatosensory evoked potentials (SEPs) in patients with multiple sclerosis.

Research by Altenmuller, Cornelius and Buettner (1990), based on scalp needle electrode recordings, demonstrated that trigeminal somatosensory evoked potentials (TSEPs), present in normal subjects, were absent in subjects with central or peripheral lesions of the central lingual pathway. The authors also reviewed previous research in which trigeminal somatosensory evoked potentials were shown to be a useful tool in the assessment of infra-orbital and inferior alveolar nerve damage.

Soutstiel, Feinshod and Hafner (1991) reported the recording of a very short latency trigeminal evoked potential in response to electrical stimulation through the use of needle electrodes (J. Soustiel, personal communication, May 1999) in the upper lip in healthy subjects. The EP consisted of 5 distinct peaks within a 12 ms period. The first part of the wave, identified as T1, was recorded as a relatively small amplitude positive wave occurring at 0.08 ms; T2 was a deep negative deflection occurring at 1.7 ms; T3 was the main feature of the response, namely a large positive wave occurring at 2.9 ms; T5 was a

negative peak at 4.9 ms while T7 was a relatively small positive wave occurring at 7.2 ms. The authors concluded that the T3 peak gave the evoked potential pattern its most notable landmark, in terms of peak amplitude, which would be especially meaningful for clinical purposes (Soutstiel, Feinshod & Hafner, 1991).

Soutstiel, Feinshod and Hafner (1991) compared their normative short latency trigeminal somatosensory evoked potentials to those elicited from patient subgroups with trigeminal nerve injury or with direct or indirect injury to the brain stem. In the subgroup with trigeminal nerve injury, an increased T2 latency with a dependent prolonged T1-T2 relative interpeak latency difference was noted. In the subgroup with brain stem injury, the main finding was a prolonged T2-T3 interpeak latency difference. It should be noted however that the brain stem subject group was comprised of a rather heterogeneous population, consisting of individuals with either tumours, haemorrhages or infarctions.

Based on the concurrence of their findings with previous early trigeminal somatosensory evoked potentials, Soutstiel, Feinshod and Hafner (1991) posited that T1 may be assumed to be generated in the peripheral aspect of the trigeminal system, most probably in the vicinity of the gasserian ganglion. Based on the short interpeak latency difference, T2 was assumed to be generated by the trigeminal nerve root close to the brain stem. T3 was felt to represent the response of the main sensory nucleus to the stimulation. This presumption was based in part on the finding of changes in both amplitude

and latency when the stimulus intensity was increased, a phenomenon evident in the auditory brain stem evoked potential literature. T5 and T7 were hypothesized to originate in the upper structures of the trigeminal system, such as the medial lemniscus and the ventral postero-medial nucleus of the thalamus.

These findings illustrated that somatosensory evoked potentials could be utilized as an indicator of trigeminal conduction en route to the brain. The challenge remained to determine the nature of the relationship between the trigeminal pathway and the processing of that signal en route to the somatosensory cortex.

Review of existing TSEP procedural detail

Review of the available published studies involving trigeminal SEPs indicated a pronounced lack of uniformity in the methodologies employed. Scalp recording sites, recording equipment configuration, stimulator properties, as well as the stimulation protocols all differed, making comparisons between them difficult if not impossible. Several studies utilized intracortical recording of trigeminal SEPs, often associated with or during surgical procedures, others utilized stimulator needle electrodes, while yet others utilized surface stimulator electrodes in a variety of anatomical locations. These differences made the challenge of reconciling the experimental data even more daunting. A summary of experimental detail previously utilized or attempted in TSEP recording studies follows below.

Bennett and Jannetta (1970) recorded trigeminal SEPs using gold-plated

disc electrodes affixed to the scalp. Bipolar stimulating electrodes 1 cm apart were used to stimulate sites along the maxillary gum line. Stimulus square wave pulses of 0.2 ms duration were used, with stimulus polarity reversal after 64 pulses for artifact suppression, for a total of 128 pulses per trial.

Buettner, Petruch, Scheglmann, and Stohr (1982) concurrently stimulated the maxillary and mandibular branches of the trigeminal nerve through electrodes applied across the upper and lower lips. Scalp recording was performed at C_5 or C_6 with a F_z reference using a platinum needle electrode applied subcutaneously. A stimulus of 0.1 ms duration was applied using bipolar surface electrodes with an intensity between two mA to ten mA. Two successive trials, ranging from 64 to 1024 stimuli over a 50 ms epoch, were digitized over 1024 data points. The latency of the first positive wave component, identified as P19, did not vary with a stimulation frequency between 1 to 20 Hz. The N13/P19 peak-to-peak amplitude remained near its maximum value until the stimulation frequency exceeded 5 Hz. The authors also determined that the separate stimulation of the upper or lower lips, or of the mandibular or maxillary branches of the trigeminal, resulted in a more pronounced P19 waveform, rather than a W configuration from those trials in which both the maxillary and mandibular branches were stimulated at the same time (Buettner, Petruch, Scheglmann & Stohr, 1982).

Drechsler and Neuhauser (1985) compared normal trigeminal SEPs to the trigeminal SEPs of pre- and post-operative treatment for trigeminal neuralgia. A 100 μs square wave pulse was applied to the mandibular branch

of the trigeminal nerve over the foramen mental using 6 mm diameter silver disk electrodes, with the cathode over the foramen mentale and the anode over the middle of the chin. TSEPs were recorded bipolarly from scalp electrodes placed at F_3, F_4, C_3, C_4, O_1, O_2. 128 stimuli were averaged for each trial. The 50 ms waveform was noteworthy since it closely resembled the 50 ms waveform obtained by Chapman et al (1986) and the results of the present study, discussed below. Of significance was the P23/N34 complex which had been characterized by Chiappa and Hill (1997, p. 355) as being a "thalamic signature". The P23 waveform component is thought to be generated pre-thalamically while the N34 waveform component is thought to be generated post-thalamically. Waveform components may then serve as an indicator of stimulus transit to the thalamus as well as transit post-thalamus.

Leandri, Parodi, and Favale (1985) reported early scalp recorded evoked potentials following infra-orbital nerve stimulation by two insulated steel needles inserted into the infra-orbital foramen. A 0.05 ms square wave stimulus pulse was delivered with an intensity of two to three times the sensory threshold, between 0.5 mA to 1.0 mA. Scalp recordings were obtained through the use of needle electrodes located at F_z, F_3, F_4, C_z, C_3, C_4, O_z, O_1, and O_2. Non-cephalic references were concurrently recorded from needle electrodes along the zygoma-mastoid line on both cheeks. The data was reported from approximately 0.5 s onwards with no further explanation given as to the missing epoch.

Chapman, Gerlach, Jacobson, Buffington, and Kaufmann (1986) reported

short-latency trigeminal SEPs from 16 healthy volunteers who underwent 800 trials of stimulation of a central incisor and the maxillary gingiva 1 cm lateral from midline. Gingival stimuli were delivered through two 1 mm diameter metal alloy balls, spaced 2 mm apart and mounted in the tip of a hand-held probe while dental stimulation was delivered through a 5mm diameter cylinder of conductive rubber mounted in a hand-held probe. A two ms pulse width was used for dental stimulation and a 0.1 ms pulse width for gingival stimulation. Mean stimulus intensity was reported as being 55 μA for dental stimuli and 8.6 mA for gingival stimuli. Scalp recordings were obtained from F_3-P_3 or F_4-P_4, contralateral to the stimulus. Each trial was comprised of 20 ms of baseline and 50 ms post-stimulus EEG. Their results were indicative of different waveforms arising from dental versus gingival stimulation, with the gingival waveform being similiar to other studies as to waveform components.

Barker, Bennett, and Wastell (1987) investigated trigeminal SEPs in 17 oral surgery patients with established unilateral sensory impairment of the face or oral cavity. Scalp recording was performed contralaterally to the side of stimulation using Ag/AgCl disc electrodes affixed the skin at to C_5 and C_6. Electrical stimuli less than 10 mA in intensity were delivered to the lip or gum near the first premolar area. Efforts were made to avoid visible muscle contractions but with no further elaboration. Increases in the latencies of P20, N30, and P39 were the most marked features of sensory loss, along with reductions in the peak-to-peak amplitudes of P20/N30 and N30/P39.

Leandri, Parodi, Zattoni, and Favale (1987) used surface and needle

stimulation to elicit infraorbital nerve responses in awake and anesthetized patients. Needle electrodes were inserted into the infraorbital foramen with a 1-2 mm interneedle spacing. The stimuli were 0.05 ms duration pulses delivered intraorally using two silver balls 2 mm in diameter affixed 1 cm apart in a plastic holder situated either on the upper lip at the skin-mucosa border or on the gum over the upper canine tooth. Scalp potentials were picked up by subcutaneous stainless steel needle electrodes placed contralaterally to the site of stimulation. Four recording sessions for each stimulus modality were noted. The authors report on the very early origins of P4, N5, P6, and N7 waveforms and posit subcortical locations for their generators.

Altenmuller, Cornelius and Buettner (1990) investigated trigeminal SEPs following unilateral stimulation of the tongue in 20 normal subjects and 20 subjects with lesions of the afferent trigeminal system. Scalp needle electrodes were placed at C_5 and C_6, sites between C_3 and T_3 and C_4 and T_4 with F_z as reference. The stimuli were 0.1 ms square wave pulses at an intensity 4 times sensory threshold, ranging from two mA to five mA, applied using a modified EEG earclip electrode 5mm in diameter on either side of the tip of the tongue. Stimulus polarity was changed after 256, 512, or 1024 stimulus responses were averaged over 50 ms epochs. Criteria for waveform abnormality was the absence of the recorded potential(s), or a unilateral latency increase by more than 4 standard deviations (s.d.). They did not consider differences in amplitude between sides to be pathological.

In 1991, Soustiel, Feinsod and Hafner published the scalp recording of

short latency TSEPs using silver-plated disk electrodes affixed to the ipsilateral mastoid, with a F_z reference. Data was collected from 25 healthy volunteers and 19 patients suffering from trigeminal lesions in the peripheral aspect or the brain stem. An electrical alternating polarity stimulus pulse of 0.05 ms duration was delivered to the upper lip via gold plated disk electrodes at an intensity of twice the sensory threshold. The analysis epoch was 12.7 ms with 512 stimuli being averaged for analysis with each test repeated twice for each side at every session. The authors chose peaks for analysis which were clearly identified and whose amplitude was at least twice the average background activity. A pathological response was defined as the peak latency of a wave component exceeding the normal latency by 2 s.d. With normal subjects, increasing the stimulus intensity from 2.5 mA to 10 mA increased the amplitude of the wave components and shortened their latencies. Unilateral abnormal TSEPs were seen in patients with various pathologies while the contralateral healthy side often produced normal TSEP waveforms. They characterized five waveform peaks within the first 12 ms post-stimulus, with the earliest occurring at 0.08 ms post-stimulus.

Soustiel, Hafner, Chistyakov, Barzila, and Feinsod (1995) investigated 40 minor head trauma patients using brainstem trigeminal and auditory EPs. The patients were evaluated within the first 48 hours following hospital admission and again at 3 months post-injury. Silver disc scalp electrodes were affixed over the mastoid ipsilateral to the stimulus side with a F_z reference. Alternating polarity stimuli were delivered via needle electrodes to the upper lip with a

10mA intensity over a 1.05 ms duration. The responses to 512 stimuli were averaged twice over a 12.7 ms epoch. The peak latencies of the T3, T5 wave components and the T3-T2 interpeak latency difference were selected for further analysis. Increased T3 and T5 peak latencies were noted in the injured population. Increased conduction times were evident in the injured group at three months but did not correlate with clinical outcome.

Soustiel, Chistyakov, Hafner, Youssim, and Feinsod (1996) recorded intracortical short latency evoked potentials from the upper lip from 14 patients during neurosurgical procedures. Alternating polarity 15 mA square wave electrical pulses of 0.05 ms duration were delivered through platinum needle electrodes to the upper lip. Through intracranial recording, three distinct and reproducible trigeminal short latency potentials were identified at N1.2, N 2.7, and N4.6. The N1.2 was a sensory action potential generated by the second trigeminal division at the base of the middle cranial fossa; the N2.7 was a sensory action potential conducting towards the brain stem along the extra-axial trigeminal circuit; while the N4.6 may arise from a sub-thalamic region.

One common element in the majority of published investigations has been the use of needle electrodes for either stimulation, scalp recording, or both. The use of needle electrodes introduces a whole element of biological safety considerations and precautions. Issues of needle sterility, sterile application and removal, 'sharps' precautions and participant apprehension come under consideration. Proper disposal of used needle electrodes and the increased risk of 'stick' injuries to the investigator serve to detract from their

attractiveness. The capacity to record TSEPs reliably using surface electrodes would make the use of such procedures more attractive for widespread use. Further refinement of the technical methodology allowing the replicable noninvasive recording of TSEPs would be a significant advance in trigeminal methodology.

The trigeminal nerve could be stimulated through several alternate means. Other than electrical stimulation, the trigeminal could be stimulated by mechanical means (Larsson & Previc, 1970), through chemosensory stimulation by noxious olfactory stimuli (Hummel & Kobal, 1992), or by laser (Bromm & Treede, 1984; Chen & Bromm, 1995; Beydoun, Morrow & Casey ,1997). Given the known trigeminal pathway, the absence of a thalamic response in a trigeminal SEP would be of great interest in whiplash since the trigeminal nerve pathway travels through the thalamus en route from the face to the somatosensory cortex.

Rationale and Hypotheses

Given the anatomical location and function of the trigeminal nerve subnuclei, it is posited that these structures would be susceptible to diffuse axonal injury (DAI) in flexion-extension or other types of torsional neck injury. It is assumed that individuals who have experienced a cervical strain injury would exhibit subtle alterations in the conduction through the trigeminal nerve substructures situated within the brain stem and upper cervical spine.

In order to be able to measure the subtle trigeminal responses using a non-invasive protocol, it will necessitate the refinement of existing technique, or

the development of new technique, to enable the replicable recording of trigeminal SEPs without the use of needle electrodes.

Hypothesis I

One of the primary goals of this thesis will be the exploration of the feasibility of, and the technical details involved in, the use of non-invasive surface electrodes for both stimulation and recording of reliable and reproducible trigeminal SEPs.

Hypothesis II

Based on the posited model of trigeminal injury, we would expect to find subtle alterations in the trigeminal SEP waveform components arising from stimulus transit through the brainstem en route to the somatosensory cortex of the brain. The alteration of trigeminal SEPs would likely be manifested in one of the following two ways:

1. Increased latency of the trigeminal SEP waveform components. Disruption or delay in the trigeminal conduction pathway due to diffuse axonal injury may be detectable through an increased interpeak latency.

2. Decreased amplitude of the trigeminal SEP waveform components. The amplitude of the waveform component may be reduced or even entirely absent, as seen in lesion cases, depending upon the extent of diffuse axonal injury.

Methods and Results

Given the interwoven nature of the subject matter and the methodological nature thereof, the present thesis will diverge from standard thesis presentation format. A description of the apparatus and hook-up procedures used throughout the study will be presented first. The methodology, results, and a partial discussion for each of the four main technical issues, namely stimulus delivery, stimulus artifact, cortical recording site, and stimulation electrode design and placement, will then be presented in four consecutive sections. Preliminary experimental findings between uninjured participants and whiplashed participants will then be presented with a brief discussion thereof. A comprehensive general discussion, merging all sections, will then be presented.

Apparatus

Two TENS units were initially evaluated for use in the present study. A Selectra Model 7720 dual channel TENS unit (Medtronic Corporation, St. Paul, Minn) was evaluated for use as a stimulus source. The Selectra unit was also used as the stimulus source for obtaining informed consent from participants. An EMPI model Epix VT TENS unit (EMPI Canada Inc, Montreal Que) was also tested as a stimulus source and was found to be unsuitable due to radio frequency interference (RFI) leakage.

The maxillary and mandibular stimulation sites were landmarked using a Pointer Plus microcurrent detector (Medi-Serv, Kanata, Ont). Two 8 mm diameter platinum stimulation electrodes were custom manufactured by

Technical Services, Brock University. The electrodes were slightly conical in shape arising from their being stamped out of a sheet platinum metal. The electrodes were soldered to shielded electrode leads approximately 24 inches in length. The centre electrode lead was connected to the stimulator using pin electrodes. The outer shielding of the electrode leads were twisted together and grounded to the stimulator casing by means of an alligator clip. Cortical recording electrodes were 7mm diameter gold-plated EEG electrodes (Grass Instrument Division, Astro-Med, Inc., West Warwick, RI). A grounding band was made from a ten inch long by two inch wide piece of stainless steel to which was soldered a 30 inch long piece of shielded braided conductor and terminated by a pin jack. Grass 10-20 brand electrode paste was utilized for the application of the cortical recording electrodes, the stimulation electrodes, and the ground band. Micropore brand surgical adhesive tape (3M Corporation, St. Paul, Minn) was used to adhere the stimulation and cortical recording electrodes to the landmarked positions.

A custom battery-operated constant current stimulator was constructed for the present study by Technical Services. The stimulator was designed to produce a current square wave pulse whose intensity was adjustable by means of a mounted vernier potentiometer. The stimulator was optically isolated for both safety reasons and noise suppression concerns. An optocoupler, housed inside the main amplifier, was connected to an optocoupler inside the stimulator via fibre-optic cable. The stimulator was modified during the study to enable electronic oscillation of the stimulus pulse

polarity. A battery-operated milli-ammeter was later constructed and added in series to the stimulation circuit to enable real time monitoring of the stimulus intensity.

A custom dual-channel amplifier was constructed for the present study by Technical Services at Brock University. A pre-amplifier pod, part of a previously built EEG recording system described in Segalowitz, Unsal, and Dywan (1992) was modified for single-channel recording use in the present study. A previously constructed 14-bit analog to digital conversion board, also referred to as a digital signal processing (DSP) board, was utilized for digitization of the analog TSEP data prior to storge on fixed and removable storage media. The DSP board was initially installed in a ISA slot in a 486 personal computer and was subsequently installed in a Pentium-III based personal computer. Most of the testing was done within the shielded ERP laboratory while a number of pilot tests were also performed within the Electronics Shop at Brock University. The apparatus configuration is illustrated in Figure 4.

Insert Figure 4 about here

Data acquisition software controlling the DSP board was extensively rewritten, including revisions for stimulator control, for use in the present study. Data analysis was performed using the custom written data acquisition software or through the use of ERPScore (Segalowitz,1999). Given the lack of a print option in the software, screen images were captured using screen-capture utilities. The image was then inverted in contrast, to facilitate ease in

printing and visual examination, using Photoshop 5.5 (Adobe Systems Incorporated, San Jose, California) running under Mac OS 8.61 on an Apple Macintosh 9600 G3/400. The PC applications were run on a Macintosh 9600 using Virtual PC 3.0 (Connectix Corporation, San Mateo, California).

System testing, debugging, and calibration involved the use of a Hewlett Packard model no. HP8011A external pulse generator, a Tektronix Model P6042 external current probe, a Tektronix Model 222 battery-operated oscilloscope, and a Tektronix model no. PDS544A digital storage oscilloscope. All test equipment was provided by Technical Services at Brock University.

Participants

The present study was reviewed and approved by the Brock University Ethics Committee under application #98-184. A total of 379 pilot trials were conducted using 27 volunteer participants, 19 female and 8 male, ranging in age from18 to 52. The volunteer participants were recruited from the Brock University population, including neuropsychology laboratory students and personnel as well as first year psychology students (PSYC 1F90). Participants external to the neuropsychology laboratory were granted up to three hours of PSYC 1F90 research participation credit. Participants who were not PSYC 1F90 students or affiliated with the neuropsychology laboratory were paid an honorarium of $10.00 per hour for their participation.

All volunteers were screened, either in person or initially over the telephone, for the existence of any pre-existing medical condition or previous involvement in motor vehicle accidents, sports injuries, or falling accidents. The

presence of any such pre-existing injury or medical condition would have served to exclude them from study participation as part of the uninjured subject pool. If the reported injury was whiplash in nature, their agreement was sought for addition to the injured participant pool. All participants were given the opportunity to experience the sensation of TENS stimulation, using the Selectra 7720 unit and two 7mm gold-plated electrodes on their face and/or wrist prior to granting their informed consent. No participant declined study participation due to any adverse reaction to the TENS stimulation. Participants were also advised of their right to terminate their participation at any point in the study, and were reminded of such right during the testing sessions. During the course of the study, no participant elected to terminate their participation.

Hookup Procedures

Scalp electrode sites were landmarked according to the standard 10-20 system (Jasper, 1958) and were affixed following standard EEG methodology. For cortical recording sites, 7mm diameter gold EEG electrodes were filled with 10-20 electrode paste and attached to the scalp using surgical adhesive tape. Interelectrode impedances were checked using a 10-channel impedance meter. The electrode leads were attached to a pre-amplifier pod, modified for single channel use in the present study.

The trigeminal nerve locations on the face were landmarked using a Pointer Plus micro-current detector, marked with a red wax pencil, and the skin was cleansed using an isopropyl alcohol saturated cotton ball. Two platinum stimulation electrodes, filled with 10-20 electrode paste, were affixed to the skin

with surgical adhesive tape. The leads were attached to a custom-made stimulator, and the ground lead from the electrodes was attached to the stimulator housing using an alligator clip.

A custom-made grounding band was placed on the upper forearm after the skin was cleansed with a isopropyl-alcohol saturated cotton ball. The inner surface of the ground band was copiously covered with electrode paste, carefully placed on the upper arm to avoid pinching the skin, and held in place with a double-sided velcro fastener.

To facilitate noise-reduced recording while in the event related potentials (ERP) laboratory, the overhead light was turned off. Illumination was provided by a standard incandescent light bulb in a table-top light fixture placed in the corner of the recording room. Subjects were requested to remain quietly seated during the actual recording trials, with eyes closed, and were encouraged to refrain as much as possible from extraneous movement.

The initial study protocol indicated the use of a battery-powered TENS unit as the stimulator in conjunction with the existing InStep recording software running on an older Pentium personal computer. It was readily apparent that the existing hardware/software combination was incapable of handling the rapid sampling rate necessary for the present study. For cortical EEG, a sampling rate of 256 times per second is considered to be adequate, and thus, is generally a standard parameter. To ensure adequate spatial resolution of TSEPs, a sampling rate in the range of 20,000 times per second was required, albeit only over a 20 or 50 ms epoch. The existing ERP hardware/software

configuration routinely generated stack overflow errors and 'crashed' when the sampling rate approached the specified value. Technical Services were consulted and undertook assembly of the custom hardware described earlier.

Issue 1: Stimulus Delivery

The initial study parameters specified the use of a battery-operated TENS unit as the stimulus source. It quickly became apparent that the Selectra 7720 unit was the source of high frequency radio-frequency interference (RFI) which readily contaminated all attempts at data collection. Given the advances in surface mount electronics and designs utilized in newer TENS units, an Epix VT TENS unit was also tested but was found to be a source of significant RFI. Technical Services were then requested to construct a well-shielded battery-operated stimulator to produce a square-wave pulse, which would be user-adjustable in both pulse width and intensity.

The design of the custom stimulator incorporated several safety elements: i) it was battery-powered to remove any risk of AC-power surges affecting the subject; ii) the stimulator was optically isolated from the main amplifier chassis, again out of safety considerations and to further minimize spurious noise contamination through the isolation of the stimulator ground. If a conventional ground-circuit design had been employed, it may have inadvertently provided a route for additional noise conduction through the ground circuit. The stimulator incorporated a Vernier potentiometer to allow for user adjustment of the pulse intensity. The Vernier potentiometer was visually calibrated from 0.0 to 9.9, and the current output of the stimulator was

calibrated through the use of an external current probe connected to an battery-operated oscilloscope. Table 2 details the corresponding calibration.

Insert Table 2 about here

The initial testing configuration utilized an external pulse generator to trigger both the DSP and the stimulator. That configuration was observed to introduce spurious noise artifacts into the system. In an attempt to minimize further spurious noise contamination, the software controlling the DSP board was modified to generate the signal pulse, which in turn would trigger the optocoupler and, in turn, trigger the stimulator. The calibration of both the stimulator and DSP board were periodically verified by oscilloscope comparison to known 1 μV and 10μV reference signals produced by an external signal generator.

The pulse width and the pulse frequency were user-adjustable through the software controlling the DSP board. The initial default parameters utilized were a 20 μs square-wave pulse over a 20 ms recording epoch. A ten percent pre-stimulus baseline was recorded for data analysis purposes. Due to software limitations, the pulse width could only be a fractional value of the recording epoch duration. Further in the study, a 50 ms epoch was adopted, and a 100 ms epoch was also attempted.

During initial stimulator trials, it became apparent that the artifact generated by the stimulus pulse was immense, being several hundred μV in amplitude. The artifact, illustrated in Figure 5, overloaded the amplifiers

causing significant signal distortion, especially in the time frame of interest.

Insert Figure 5 about here

It was determined through real-time manipulation during three trials that the size of the artifact could be reduced by converting the stimulator to an alternating polarity configuration. The data collection would be paused mid-way through the data collection, the stimulation electrode leads would be physically switched at the stimulator, and the data acquisition would resume for the remaining half of the trials. The average of those trials, illustrated in Figure 6, revealed a smaller, although still large and problematic, signal artifact.

Insert Figure 6 about here

It was possible for the pulse orientation to be 'flip-flopped' electronically without the need for change at the stimulation electrode level. Thus, one pulse would be positive-negative in its orientation, while the following pulse would be negative-positive. Following stimulator modification, trials with the alternating polarity configuration proceeded and, eventually, started to produce waveforms reminiscent of EEG, albeit still contaminated with artifact in the first 10 ms of data, as reflected in Figure 7.

Insert Figure 7 about here

Once the data collection had progressed to the real-time recording of

TSEPs produced by both the positive and negative stimulus pulses, it was seen that the artifact produced by the two pulses did not arithmetically cancel out. This was indicative that one of the artifacts was larger than the other, either in amplitude or duration. The difference between the two pulses was most likely due to either a stimulator defect or a biological response to the alternating stimulation polarity.

Concurrently, it was observed that the skin impedance of the face had large variations in value within the region where the stimulation electrodes were to be attached. The skin impedances were observed to range from 11 kΩ to 120 kΩ. To document the intensity of the current pulse being delivered by the stimulator while attached to a participant, the magnitude of the current pulse was measured in real time, again using an external current probe and a portable digital oscilloscope. The magnitude of the current pulse was verified in real-time, after considerable hardware tinkering. However, the hardware set-up to do so was cumbersome and would have increased the opportunity for experimental error. Since the current measurement needed to be performed during each trial with each subject, a more efficient method had to be devised.

To address these concerns, an analog mA current meter was constructed and inserted in series within the stimulation circuit. The addition of the meter enabled the real-time monitoring of the current flow through the stimulation electrodes. A capacitive circuit was also built-in to the meter to allow for smooth meter movement. Otherwise, the meter movement would have been rapidly alternating in response to the 50 μs pulse, making accurate

visual reading of the meter virtually impossible.

With the addition of the current meter to the stimulation circuit, it was quickly determined that, as had been suspected, the stimulus level was not constant between subjects. In individuals with high skin impedance, the stimulator was incapable of delivering the expected level of current output. The level of stimulator output, as the intensity was being increased, was seen to actually decrease due to the breakdown of the stimulator current output capacity. It was evident that the stimulus intensity could not be approximated but had to be measured in real-time to ensure that the expected level of stimulus intensity was equal to the actual level of stimulus intensity being delivered through the stimulation electrodes. To ascertain whether or not the stimulator was indeed able to generate the expected intensity, a digital storage oscilloscope and the external current probe were used to record the characteristics of the current pulse under various loads.

To also address the question of the artifact differential, the stimulator was connected to a fresh leg from the common chicken, *Gallus domesticus*, a tissue which resembled human tissue in its biological properties. Figure 8 represents the current square wave pulse generated by the stimulator while connected to the chicken thigh. It was evident that the stimulator was operating as designed.

Insert Figure 8 about here

When the stimulator was increased to almost its maximal value, the 40

mA waveform retained the normal square wave shape. It was evident that the stimulator was functioning as intended in the stimulation of biological tissue. The last alternative to be documented was the stimulator response when attached to living, biological tissue.

Insert Figure 9 about here

Figure 9 represents the stimulator response when attached to a human inner forearm, medial from the wrist, under a 10 mA pulse of 50 µs duration. The square waveform was self-evident.

Insert Figure 10 about here

Figure 10 represents the stimulator output under a 20 mA pulse of 50 µs duration. The breakdown in the stimulus pulse was self-evident in the latter half of the pulse. The waveform pattern was indicative of a capacitive effect in the skin, at the site of stimulation, as a response to the polarizing of the skin by the stimulus pulse. Over the trials, the time frame for return to baseline was consistent across subjects at the stimulation levels employed by the present study. Given its consistent nature, it was decided to proceed with the study, with the capacitive skin effect being a known confound across subjects.

One of the last factors to be explored was the degree of trigeminal response to the magnitude of stimulation. In the present study, the intent was to adequately stimulate the trigeminal nerve so as to produce a somatosensory response while minimizing artifact or other confounds. The presence of muscle

twitching would have served to contaminate the signal, as Figure 11 illustrates. The single trial frame represents EMG or muscle activity due to participant movement. Pronounced muscular movement only served to contaminate the TSEP waveform.

Insert Figure 11 about here

The amplitude of the current pulse had been observed to affect the degree of neural response. Initially, a current setting of 10 mA was employed in the present study. Once the feature became available in the software to allow for the frame-by-frame review of the data, the 10 mA pulse was noted to elicit a neural response in a small number of trials. During single frame review of the data, the TSEP was seen to be fairly robust in that the 'fires', i.e. those trials in which a trigeminal response was evident, could be visually differentiated from the 'non-fires', or those trials in which a trigeminal response was absent. Figure 12 illustrates this visually. The top frame captures a 'fire' TSEP waveform. The N19 and P27 are visually discernable in both of the pulse trains, as well as in the arithmetic average of the two trains (the middle waveform trace). A 10 mA pulse intensity would typically produce a neural response rate between 20 to 30 percent. Thus, in a trial with 512 stimuli, only roughly 100 to 150 trigeminal responses would be evident. In and of itself, this was not an immediate concern given the robustness of the TSEP, which was discernable after as few as 128 trials. What was of concern was the diluting effect on the TSEP through averaging with more 'non-fire' noise trials than actual 'fire' trials.

Insert Figure 12 about here

In 12 trials over six sessions, a 100 μs stimulus pulse width was evaluated. The participants uniformly reported that the 100 μs stimulus pulse width as being uncomfortable. A 50 μs pulse width and a 15 mA stimulator setting were then evaluated over 14 trials over seven test sessions. Those parameters produced TSEPs of higher amplitude but also produced visible twitching of the *oris orbicularis* musculature. Subjective reports described the 15 mA stimulus intensity as definitely noticeable in addition to sensations from the muscular twitching. The 15 mA stimulus setting was not utilized further, not only out of participant comfort concerns, but also due to the verifiable confound of muscular twitching.

An intermediate stimulus intensity of 12 mA was then tested over ten trials and was found to be effective. The combination of 12 mA intensity over a 50 μs pulse width increased the trigeminal response rate in normal participants to between approximately 50 to 60 percent while avoiding muscular twitching and pronounced subject discomfort. No participants expressed any discomfort at the 12 mA setting, even if prompted to do so. The typical description was one of a 'tingling' sensation to which they quickly became accustomed. The 12 mA stimulus intensity was adopted for the remainder of the study.

Discussion - Stimulus delivery

Accurate and adequate stimulation of the trigeminal nerve was a

fundamental requirement of the study in order to allow for any meaningful comparison both within- and between-subjects. Previous studies (Leandri, Parodi, & Favale, 1985) had documented increased neural response to larger current stimuli which were reflected in larger SEPs being produced in response to the larger stimulus. However, the stimulus intensity could not simply be increased in order to elicit a more pronounced TSEP. Extra care had to be exercised for several reasons. Firstly, the face is one of the most highly innervated regions of the body and thus care had to be taken to minimize participant discomfort and any related muscular movement arising from that discomfort. Secondly, and equally important, one did not want the stimulus pulse to be of such a magnitude so as to generate efferent muscle activation. Eye blinks would have been problematic given the proximity of the eye muscles to the recording electrodes, especially F_z. It had also been noted that eye blinks could serve to mimic early TSEP waveforms (Leandri, Schizzi, & Favale, 1994). The easiest solution to these concerns was achieved through the instructions given to the participants. They were requested to sit quietly with their eyes closed during the stimulation testing trials. Participants were then invited to stretch about or move around in-between the recording trials. These simple precautions were sufficient to minimize, although not totally prevent, movement artifact or eye blink contamination. The presence of movement or eye blink artifacts would then be detected during the frame-by-frame review of the results, as discussed in following sections, allowing for the elimination of movement contaminated trials from the average waveform.

Since the pulse width could not be increased due to hardware and software limitations independent of the recording epoch, a pulse width of 50 μs was available only on a 50 ms recording epoch or less. Likewise, a 100 μs pulse width could only be obtained on a 100 ms recording epoch. Increasing the recording epoch from 50 ms to 100 ms had the disadvantage that the number of DSP sampling points (1024) would now be spread over twice as much data, with an ensuing loss of resolution. The loss of resolution may have proven problematic during post hoc signal processing, especially for noise filtration aspects.

Stimulus polarity emerged as an important issue as well. Based partly on the experimental trails, the magnitude of the stimulus artifact could be reduced through alternating polarity of the stimulus pulses. In order to alternate the polarities, one could have done so either by modifying the electronic circuitry to alternate the polarity, or one may have been able to physically switch the electrodes. The latter would have been challenging given the stimulus rate. Basic operational dynamics would have prevented this approach, as it would have been impossible to alternate the electrode connections physically at a rate of four per second. During the pilot trials, it was only feasible to collect one-half of the trials in one polarity configuration and then switch the electrodes. This would not have been the preferred choice as it would have allowed the skin to undergo a polarization process during the same-polarity stimuli.

Although the stimulation pulses were being rapidly alternated, a skin polarization effect was still apparent, most likely due to ionic processes within

the skin (McGill et al, 1982), which then took a period of time to dissipate and return to baseline. This was a biological property of the participants skin and would have been impractical if not impossible to control for. Given that the extent of the capacitive effect was constant across subjects at the stimulus intensities utilized, the study proceeded with the capacitive effect as a known confound across subjects. The nature of the capacitive effect, if any, on the degree of neural response would need to be documented more extensively in future research.

A number of other important issues also came to light during the present study. Rather significant was the observation that, while using a constant-current device, the skin impedance of the subject can affect the current magnitude being delivered to the electrodes. Since the variation in skin impedance was so pronounced, it raised concerns as to the uniformity of the stimulus. Given that the stimulator employed a constant-current design, such a large variation in skin impedance would affect the amplitude of the stimulus pulse, such that in those individuals with high skin impedances, the stimulus intensity would be, of necessity, less than in those individuals with lower skin impedances. Using a fixed oscillator output voltage of 60 V arising from safety and subject comfort concerns, the stimulator circuit would have specific limits within which it would be able to generate the expected pulse intensity. Following Ohm's Law, when the resistance in the stimulator circuit, through the skin impedance, was significantly higher than expected, the only possible outcome would be a decreased stimulus intensity.

A significant hurdle thus arose in that one could not be confident that the stimulus intensity would be uniform across subjects, or even across stimulation sites. Uniform stimulus intensity both within- and between-participants would be a crucial requirement for a reliable measure. Since large skin impedances would have decreased the stimulator current output, one would have needed to reduce the skin impedance or increase the output capacity of the stimulator. To alter the output capacity of the stimulator would have required a complete redesign of the stimulator circuitry to prevent the current pulse breakdown. In order to do so, it would have also necessitated increasing the oscillator voltage within the stimulator to a value greater than 60 V. Such an increase would have increased subject discomfort since the trigger voltage influences the sharpness of the stimulus. With the in-line current measurement capability, it was determined that the stimulator output could be kept within an acceptable range, so as to prevent overloading of the stimulator and the associated breakdown of the stimulus pulse, for the stimulus intensities utilized in the present study. The present stimulator design was retained for the remainder of the study.

One drawback of the stimulator design employed, evident after its construction, was the non-linear output of the square wave pulse. The stimulator output increased exponentially toward the end range of the potentiometer, with a rapid rise in current output evident from a setting of eight onwards on the Vernier dial. The problem therein was that, given the stimulation range utilized in the present study, a small change in dial position

could result in a large difference in the amplitude of the square wave pulse being generated. The use of in-line current measurement enabled more accurate control of the potentiometer setting. The present stimulator design could continue to be utilized with the use of the in-line milli-ammeter.

Although a number of the previously cited TSEP studies have utilized a constant-current stimulator, none of them utilized an in-line current measurement instrument or protocol. Even though the calibration of their stimulator had most likely been carefully checked *in vitro*, the lack of *in vivo* measurement of skin impedances during stimulation or the lack of real-time current measurement could pose serious limitations. The greatest limitation to those study results would be due to the question of whether or not the actual intensity of nerve stimulation was the same as the experimentally expected value.

Combined with variation in the degree of skin abrasion during site preparation, irregularities in the application of the electrolytic paste, the amount of sub-cutaneous adipose tissue, as well as the degree of sweating and interference from body hair, the accuracy of surface stimulation (Bronzino, 2000) cannot simply be taken for granted. At the very least, adequate care must be taken to ensure uniform site preparation and electrode application, both between electrode sites as well as between subjects, to help minimize the introduction of further confounds of factors which could otherwise be minimized. Since the primary stimulation site was located on the face, it was not amenable nor practical to perform significant skin abrasion in order to

reduce the skin impedance at those sites. In addition to the subject's apprehension, one would not want to inadvertently introduce an experimental confound by significantly irritating the skin in the target area prior to the experimental stimulation.

Issue 2 - Stimulation Artifact

The initial scalp recording sites were modelled after scalp sites routinely employed for cortical EEG recording. The main cortical recording electrode was placed at F_z with a contralateral mastoid reference and earlobe ground. Data collection consisted of 256 trials arithmetically averaged using a 20 μs stimulus pulse over a 20 ms recording epoch. Ten percent of the recording epoch was utilized as a pre-trigger baseline. Interelectrode impedances were kept below 5 kΩ. The initial results, presented in Figures 21 through 23, were indicative of significant artifact problems early in the recorded waveform masking any early waveform components, once a suitable amplification level had been achieved.

The amplifier gain factor had initially been set at 20,000 times, based on the existing cortical EEG standards (Bronzino, 2000). Figure 13 represents one of the initial trials at the original gain setting. Although the artifact was not problematic, the absence of any waveform thereafter was problematic. Noting the large scale indicator, it illustrated that data was virtually non-existent at that amplification level, other than artifact. That was not an overtly surprising observation, given that the desired TSEPs were typically in the range of 1-2 μV in amplitude.

Insert Figure 13 about here

Review of the initial results necessitated an adjustment of the gain setting of the main amplifier. The amplifier gain factor was adjusted to 100,000 times, based on a review of the amplifier settings employed in the existing SEP literature (Chiappa, 1997).

Insert Figure 14 about here

In Figure 14, the stimulation artifact was evident in the first 10 ms of data. It was also apparent that the electronics were being overloaded by the magnitude of the stimulus artifact. Figure 15 represents the stimulus artifact over a 50 ms epoch. The data indicated stimulus artifact and little useful signal over the rest of the recording epoch.

Insert Figure 15 about here

To explore the role of gain in artifact generation, a number of *ad hoc* trials were performed. Through this process it was discovered that the initial gain calibration in the main amplifier was incorrect. The gain factor was to have been 200,000 times but erroneously was over 300,000 times. Once corrected, signal reminiscent of EEG began to appear in the waveforms from 10 ms onwards, although the artifact was still present. Figure 16 illustrates a 50 ms trial after the gain correction.

Insert Figure 16 about here

To address the massive artifact, several areas were explored. After a period of *ad hoc* testing, it was determined that the massive artifact was due to the saturation of the band-pass filters employed within the amplifier. Numerous filtering combinations were tested with similiar results such that the artifact would still overload the filter combination. A standard 60 Hz notch filter was also tested and was seen to produce filter artifact.

To overcome filter overloading, it was necessary to eliminate the band-pass filtering within the electronics. Further trials following removal of the band-pass filters revealed further contamination issues. The results revealed a rapidly oscillating waveform present for the first 2-4 ms of data which was identified as a phenomenon known as amplifier ring. The amplifier circuit was being overloaded by the magnitude of the stimulus artifact, typically requiring 2-4 ms to decay back to baseline levels.

Insert Figure 17 about here

Figure 17 represents a trial over a 20 ms recording epoch with significant amplifier ringing present within the first 3 ms post stimulus. The overloading of the amplifiers also created distortion in the remaining data rendering it unreliable. The presence of high-frequency contamination was also evident by the overlay on top of the slower rolling waveform.

Figure 18 represents another trial with amplifier ring still evident. The filter ring had abated within 3 ms and several waveform components were starting to emerge. It was noted that the waveform components appeared to be increasing in relative amplitude over time, slowly returning to baseline levels. After prolonged troubleshooting, it was discovered that an AC coupling circuit within the amplifier acted as a filter which, when overloaded, introduced a slow-decay noise overlay onto the recorded data.

Insert Figure 18 about here

Following the disconnection of the band-pass filtering circuitry, the recording system became more susceptible to spurious noise. During ensuing trials, RFI contamination, both high frequency components as well as a low frequency 'roll', became immediately evident within the data, even with the use of the specially-constructed stimulator. In unreported trials, one could visibly observe the noise rolling across successive data acquisition frames. Figure 19 represents the raw average of one such noise-contaminated trial.

Insert Figure 19 about here

Using hand-held RFI detectors, the degree of RFI present within the ERP laboratory was explored. One identified source for high-frequency RFI were the older-style computer monitors used in the lab. It was determined that when the monitor was placed in the adjacent equipment room, it would be far enough removed from both the subject and the recording amplifiers so that its RFI

contamination would be negligible. The monitor could still be used for the present study as it was positioned in front of the two-way mirror situated between the two rooms. The RFI contamination from the other computer monitors present in the lab could be eliminated if they were turned off prior to data collection.

The degree of RFI from other sources within the ERP lab was also noted and adjustments were made as necessary. As one example, the overhead light was identified as a source of 60 Hz RFI preventing its use during data collection. During data recording, the lab was illuminated using a 40W light bulb in a table lamp in the corner of the lab. In that location, it was far enough removed from the subject and the recording equipment so as not to be a problematic source of RFI. Electrical conduits installed along the outer surface of the inside walls of the ERP lab were also identified as RFI sources. Through the use of real-time experimentation, approximate boundaries were identified wherein a seated subject could be positioned to minimize the 60 Hz RFI from the electrical conduits.

It had been noticed that decreasing the interelectrode impedance of the scalp recording electrodes improved the quality of the waveform components. Instead of electrode impedances being below 5 kΩ, interelectrode impedances below 2.5-3 kΩ were seen to be beneficial in terms of signal quality. Figure 20 illustrates one such waveform obtained at the lower impedance. The presence of a negativity in the waveform at 6-7 ms was encouraging, the presence of amplifier ring was still evident.

Insert Figure 20 about here

In Figures 17-20, the amplifier ringing was off scale and data clipping had occurred at the maximal values. The clipping indicated that the DSP had been 'railed', or overloaded such that the data was being clipped at the maximal DSP value. Between 1-2 ms, the DSP had recovered from saturation and amplifier ring was evident as the signal slowly returned to baseline values. Because of the DSP clipping, the gain was subsequently reduced by a factor of two to a new gain factor of 100,000 times and the system was re-calibrated against known reference signals.

Given the increased amplifier lag, a further modification was undertaken in that the pre-amplifier chip in the pre-amplifier pod was replaced with a newer, lower noise DC broad-band amplifier integrated circuit which had a faster overload recovery time. In subsequent trials, this modification proved beneficial in that the amplifier recovery window was shortened dramatically, often to 1-2 ms.

Once faster amplifier recovery was achieved, it served to confirm that the presence of artifact continued to prevent any meaningful resolution of the first 5 ms of data. Further bench-top testing indicated that the artifact could be further reduced if the alternating polarity stimulus pulses were recorded separately and then mathematically averaged together. Figures 21 and 22 illustrate two such trials. The artifact, although still present, was limited to within 3 ms post-stimulus. Replicability of the waveforms had become problematic since

Figures 21 and Figures 22 represent two successive trials. The two successive waveforms were different from each other in appearance but were also phase shifted relative to each other. The same discrepancy was evident over the next 35 trials, confirming the poor replicability of the waveform.

Insert Figures 21, 22 about here

A programming error was discovered within the acquisition software which controlled the incoming data. The error concerned the accumulation of the data from the separate pulse trains, resulting in an arithmetically incorrect summation of one of the two waveforms. The software was also modified to save the individual trial data to hard disk. The previous approach held the raw data in the DSP accumulator memory until it was averaged and then stored to disk as an averaged file. Previously, it was observed that the data had become corrupted during the acquisition period in a number of trials. Figure 23 represents such a trial in which the data had become corrupted.

Insert Figure 23 about here

Review of the averaged file revealed that a number of data points were missing from within the data file. Closer review of the other corrupted data files revealed that the missing clusters were not located at the same time points within the average, nor were the missing clusters of uniform size. The missing clusters served to introduce frame-shift reading errors when the data was reviewed. Given the sequential reading of the data files, the discrepancies

would simply cause the program pointers to lose their place, as reflected in Figure 23. The errors were eventually isolated arising from a defective hard drive in the personal computer used for data acquisition.

After the recording system bugs had been corrected, it was demonstrated that the stimulus artifact could be averaged out to a greater degree than had been evident before by mathematically averaging the separate data from the positive and negative stimulus pulses. Figure 24 illustrates the two pulse trains while Figure 25 illustrates the arithmetic average of the two pulse trains.

Insert Figure 24 about here

In Figure 24, the stimulus artifact was well defined and was seen to return to baseline within 5 ms. The TSEP waveform was evident, especially the component peaks occurring at N19 and P27. In the average, the downward shift between the pre- and post-stimulus baselines arose from a mathematical artifact generated by the slight difference between the pulse widths of the two pulse trains.

Insert Figure 25 about here

Figure 25 illustrates the mathematical average of the positive and negative pulse trains illustrated in Figure 24. The stimulus artifact, as in this example, was seen to reasonably cancel out. The P13, N19, and P27 component peaks were evident and well-defined. The question of whether 60Hz noise was present arises given the sinusoidal appearance. The

periodicity of 60 Hz noise would be approximately 16.67 ms while the peaks at 19 ms and 40 ms would create a periodicity of 21 ms, equivalent to a frequency of approximately 48 Hz. While direct 60 Hz noise contamination was unlikely, there may have been contamination due to harmonics of the 60 Hz noise.

Discussion- Stimulus artifact

The largest and most frustrating issue arising from the surface recording of TSEPs were the problems arising from stimulus artifact and the response of the electronics to the artifact. Given that TSEP waveform component amplitudes range from 0.3 - 2.0 μV, they would easily be obscured by artifact whose amplitude was typically in excess of 150 μV. The issue would be compounded by the problem arising when the electronic circuitry, designed to differentiate a 1-2 μV signal, would be overwhelmed by an artifact which was orders of magnitude greater than the target signal. The close proximity of the stimulation and recording electrodes may generate a high amplitude stimulus artifact, completely destroying the short latency TSEP from being clearly resolved (Drechsler & Neuhauser, 1985).

The stimulus artifact was problematic not only for the amplification circuitry, but also for other circuit components typically found in EEG recording equipment. Other components downstream from the amplifiers also exhibited erratic behaviour post-artifact. The stimulus artifact may best metaphorically be compared to a tidal wave, overwhelming structures in its past simply by its sheer magnitude.

The amplifiers employed in EEG apparatus were typically low-noise and

fast recovery in their design. To minimize spurious noise contamination, most EEG configurations employ low-pass and high-pass filters designed to allow the desired frequency ranges to pass through while blocking unwanted frequencies. In the present study, both of these typical system constituents proved to be problematic given the stimulation artifact. Resolution of the technical challenges proved to be difficult since the resolution of one issue only served to shed light on the existence of further challenges.

The use of band-pass filters proved to be problematic. On the one hand, the use of filters led to data distortion through the overloading of the filters by the artifact; on the other hand, removal of the filters made the recording system sensitive to undesired frequency contamination of the data. The effect of the stimulus artifact on the filter circuits was responsible for the loss of usable data during the time window required for the filter to return to baseline. The size of the filter overload caused by the artifact was of such magnitude that the small TSEP signal could not be resolved and was for all purposes lost within the filter artifact. The artifact created did exhibit a small positive benefit during equipment debugging. It was discovered that a filter circuit had inadvertently been left connected within the main amplifier. The filter artifact overlay was evident in some of the 50 ms trials with the waveform slowly returning to baseline, with the waveform following an approximated exponential decay curve. The ability for an exponential decay function to be accurately mapped onto the recorded waveform (Emerson, Sgro, & Stanton, 1988) indicated that the circuit was still both operational and affecting the data. Following the lead

from the data, the electronics were rechecked and the circuit was discovered.

The time requirement for the filters to stabilize after being overloaded precluded the recording of any useful data in the first 10-15 ms of the recording epoch. That was highly problematic in that the early brainstem response to trigeminal stimulation occurred within that time frame. The absence of waveform components within the recorded waveform served as further confirmation since there should have been, based on the SEP literature, several waveform components between 5-20 ms.

Following the removal of the in-line band pass filtering, the recording system became very susceptible to spurious RFI and line noise. In the process of identifying and eliminating RFI sources within the lab, a number of unexpected RFI sources emerged. When one is interested in measuring brainstem responses, one would not normally consider sources such as light bulbs and computer monitors. While the lower illumination in the main ERP lab was helpful by allowing the monitor placed in the adjacent room to be seen clearly enough to continue its usage, the fact of needing to do so indicated the degree to which RFI was explored in the present context. In the initial construction of the main amplifier, it had been designed such that it was 'AC-coupled' to help re-centre the recorded data onto the specified baseline. Instead of being beneficial, it served to introduce further 60 Hz line noise into the system following removal of the band-pass filters. A nine-point sliding average filter was utilized to help remove high frequency contamination from the averaged data.

Improvements in procedural detail were beneficial in reducing RFI contamination. As noted earlier, cortical electrode impedances were critical to the recording of minimally contaminated data. The cortical electrode impedances were determined to allow for the cleanest signal recording if the impedance values were kept around 1.5 kΩ, a significant increase when compared to accepted EEG procedure. During data collection, the appearance of high frequency noise was an indicator of increasing electrode impedances due to a weakening of the electrode adhesion to the scalp. Typically, the electrode became unaffixed due to tape adhesion weakening, subject or hair movement, or electrodes being inadvertently pulled off due to subject or experimenter movement.

The ground band impedance was also an important part of the signal-noise equation. It had been observed that the ground band impedance was related to the presence of low frequency, including 60 Hz, noise within the data. Typically, poor ground band application onto the forearm resulted in higher electrode impedance which in turn was reflected by the presence of low frequency noise. The desired ground band impedance being kept below 2 kΩ allowing for relatively clean recording. When the ground band impedance values were higher than 2 kΩ, it would be manifested by 60 Hz overlaid onto the data. Following the principle demonstrated with the cortical electrodes, low frequency noise would begin to appear in the data if the ground band impedance began to increase during data collection. The ground band may have loosened due to improper application or even subject forearm muscular

movement.

Following the identification of filter artifact, amplifier artifact then emerged as being problematic. The amplifier artifact was most likely present but obscured by the filter artifact, strengthening the signal distortion argument. The amplifier artifact was addressed through the change to a newer, lower noise and faster recovery amplifier chip in the pre-amplifier pod. The artifact was also addressed arithmetically by averaging the opposite polarity pulse trains together, effectively cancelling the artifact.

However, since the two artifacts were of slightly different duration, as a response of the skin's capacitive effect, as outlined previously, the residual artifact was to be expected. As a precaution to address the residual, only data after 5ms post-stimulus would be considered to be valid data. Given that unsolvable obstacle, it was decided to concentrate the data collection using a longer 50 ms epoch which would then allow for the recording of mid-range TSEP waveform components, indicative of pre- and post- thalamic processing, rather than only early brainstem waveform components. In the event that the early waveform recording issues were unable to be overcome, one would at least be able to explore between-group differences in terms of the thalamic response.

More importantly, the waveform components being recorded corresponded to earlier published TSEP and median nerve SEP waveforms. The three waveform components, specifically the P13, N19, and P27 became central in the evaluation of the data, in that they were representative of a

thalamic response (Chiappa & Hill, 1997) as well as conforming to previously published studies (Dreschler & Neuhauser, 1985; Chapman et al, 1986). Those observations indicated that the present system had been debugged sufficiently and technical hurdles had been overcome to enable the surface recording of replicable waveforms without the use of needle electrodes, reaching an important milestone in the study. The successful cancellation of the stimulus artifact was a product of carefully controlled electrode impedances, stimulus intensity, location of stimulating and recording electrodes, as well as improvements and modifications to what no longer could be considered a standard EEG set-up.

The recording of the raw trial data to hard disk in real-time allowed for the off-line review of each stimulation pulse for each trial, enabling a more detailed examination which would not have been possible with only overall averages. Such review also enabled the rejection of blink or movement contaminated trials and the determination of the neural response rate. The real-time recording of raw data also prevented the total loss of the data from that trial should there be software or hardware crashes, which unfortunately had occurred several times during the course of the present study.

Other technical glitches experienced during equipment debugging included the early realization that the DSP had been incorrectly calibrated in its analog to digital conversion programming. Although corrected, it prevented any meaningful comparison of the peak-to-peak values from the data which had already been collected in the early stages of development. Nonetheless, the

data were still useful for documenting the technical difficulties which had been encountered.

The one-channel recording limitation of the present system was extremely challenging. Instead of being able to record in real-time from several cortical sites, as is often done in SEP studies (Chiappa, 1997), the present system only allowed for one-channel recording. To offset that limitation, the experimental protocol was modified to include the recording of a 'noise trial', in which the subject would remain seated quietly as before, with the exception of the stimulator not being turned on. This provided an electronic noise baseline within the testing environment, perhaps allowing for post hoc signal processing to remove a portion of the noise from the TSEP. Noise reduction was an important consideration since trials could easily become contaminated by RFI, rendering the ensuing data virtually useless. Although far from ideal, and concerns arising from the use of one static noise control for many testing trials, there would have been potential in exploring different avenues of post hoc noise filtering. Testing was terminated prior to the implementation of these types of techniques.

Another significant issue emerged during trials in which electrode impedances climbed during the trial, thus beginning to corrupt the data during the recording. The present system was incapable of displaying the real-time average of the data as it was being collected. In essence, one had to wait until the end of the trial to evaluate the data just collected. As the trial would not then be repeated due to operator presumption of usable data being collected, this

lead to gaps in useable data. Given the capabilities of the present equipment, the only other alternative would have been the review of the entire data set immediately after collection. Since this was a time-intensive task, it too was impractical as it would have required long pauses between each trial, prohibitively prolonging the total participant time requirements. It may have also opened the opportunity for additional complications to develop. The electrode paste had a tendency to start drying out and therefore increase electrode impedances after roughly one to one and a half hours. The time required to manually review the data would have then necessitated the continual monitoring of electrode impedances and the possibility of being required to reapply electrodes an additional number of times. Further improvements in the real-time monitoring of both data acquisition and electrode impedance changes would be advisable.

As mentioned, a beneficial improvement to the software would enable the real-time monitoring during data collection. With the present system, one was unable to display the averaged waveform once data collection had commenced. The averaged outcome would only be known following manual review of the averaged waveform file on the monitor. The present software could not allow for the real-time display of the data for two main reasons. First, the software could not display the collected waveform in real-time at a usable scaling. Although the software was capable of vertical scale adjustment of the data, in effect amplitude resolution, it could not do so in real-time. If one were to adjust the scaling to the μV range needed to visualize the TSEP, the display

would have been either blank or filled with jumping images. Due to problems with the way the software handled the DC offset of the data, it could not keep it centred on the screen at the smaller scale settings required to visualize TSEP components. Generally, only during the maximum scale setting of +/- 350 μV would the EEG remain centred on the display. At that scale setting, only the massive skin artifact could be visualized. The use of the maximal scaling did allow the operator to detect serious noise contamination since it could be visualized rolling across the display. It also allowed the operator to verify the presence of the artifact, which evolved during the course of the study to serve as a visual cue that the stimulator was working and that the recording preamplifier pod had been placed on-line.

Second, the software and DSP were programmed to accumulate the data and to only average it at the end. The capacity for real-time averaging would have been highly desirable to enable the operator to see the waveform emerging during data collection, rather than having to wait for the result until the end of the trial. These two changes would have made the software much more user friendly in terms of data collection and, as such, the programming changes to enable same would be highly recommended.

On the obverse, the present system had several advantages. The DSP board, having been previously designed and built by Technical Services, was a 14-bit analog to digital conversion ("A2D") card. The present configuration was one of the highest-bit rate A2D cards available since many commercial A2D cards were based on only 8-bit or 12-bit conversion factors. The extra

resolution of the Brock DSP card was beneficial in providing for the ability to rapidly resolve the small amplitude analog TSEP signal. When one considered that TSEPs were typically 1-2 μV in amplitude over an event duration of 20-30 ms, it had been likened to looking for the proverbial needle in a haystack.

The advantage of having technicians available on campus in the Electronics Shop cannot be overestimated. Their local presence allowed for on-site revision and modifications to be piloted and implemented or abandoned. Remote technical support can often be slow and cumbersome and in and of itself can be a source of frustration.

Issue 3 - Cortical Recording Sites

As mentioned previously, the present study had initially utilized F_z as the recording channel with a contralateral mastoid reference and ear ground. However, combined with the electronic obstacles, the initial cortical recording sites did not produce any useable data. During a reprogramming interval, a further review of the literature indicated that many SEP studies utilized a scalp location localized over the somatosensory strip of the brain as the primary recording site. The site was landmarked as 1 cm posterior from either C_3 or C_4 (Chiappa, 1997), and was identified as C_c for contralateral recording sites and C_i for ipsilateral recording sites. C_c was specified as a fixed measure, instead of a percentage measurement as in the conventional 10-20 system. In the present study, those sites were adopted and were hence identified as C_{cl} or C_{cr}, on the left side or the right side, respectively. Following the change to C_{cl}

and C_{cr} as the primary recording sites and the revision to the DSP programming, the replicability of the TSEP waveform increased substantially.

With the adoption of the C_c recording sites, the characteristic waveform became more robust and discernable. Figure 26 illustrates one of the early TSEP waveforms obtained during equipment and software debugging. Of particular note is the presence of slight positivity at 13 msec, hence referred to as P13, an evident negativity at 19 msec, referred to as N19, as well as a positivity at 27 msec, referred to as P27.

Insert Figure 26 about here

The cortical recording sites of C_{cl} and C_{cr} were routinely employed with the recording site being contra-lateral to the side of stimulation. As discussed previously, the recording electrode impedances were determined to be of critical importance. If the electrode impedances were too high, then the recorded waveform would be contaminated by the presence of high frequency noise. Thus, the accepted standard impedance for cortical EEG electrodes, typically 5 kΩ or less, was determined to be unacceptable for the present study. It was determined over the course of the pilot data collection that cortical recording electrode impedances had to be below 2 kΩ, with a desired range of 1.2 - 1.8 kΩ to ensure a good TSEP waveform.

Insert Figure 27 about here

Figure 27 illustrates high frequency contamination due to poor cortical electrode impedances. Figure 28 illustrates the same data set as in Figure 27, but after the application of a nine-point rolling filter. Although the use of the rolling filter was advantageous for the removal of high frequency contamination, there were practical limits to that ability. Figure 28 illustrates the remaining high-frequency contamination of the data set following application of the nine-point filter, whose continued presence in the data rendered it unusable. All trials were processed using a nine-point moving average filter, so the utility of the noise filtering achieved by such a procedure would be evident, especially in later trials as illustrated in Figure 37.

Insert Figure 28 about here

The importance of scalp landmarking accuracy became evident. If the scalp electrodes were off slightly from their intended positions, the recorded waveform would be quite different. In one trial, a student assistant made a measurement error while landmarking sites on the scalp with the net result that C_{cr} and F_z were anterior by approximately 1 cm. Figure 29 illustrates the two pulse trains recorded during that trial.

Insert Figure 29 about here

Figure 30 illustrates the mathematical average of the two pulse trains illustrated in Figure 29. In comparison to Figure 26, the difference between

waveforms was evident. Figures 29 and 30 also illustrate the improvement made with respect to the stimulus artifact. In Figure 29, the artifact was evident as a defined pulse which returned to baseline within the first 5 ms post-stimulus. In Figure 30, the cancellation of the two pulse artifacts produced a reasonably clean cancellation of the skin artifact, rendering clean data from 5 ms onwards. Within the many unreported trials performed, the artifact could be cancelled out as early as 3 ms. To err on the side of caution, the longer 5 ms time interval was considered to be the artifact-free threshold.

Insert Figure 30 about here

Apart from the primary cortical recording site, the location of the reference and ground electrodes were also re-evaluated. Through ad hoc testing, it was determined that the ground electrode was too close to both the stimulation and recording electrodes. A new grounding electrode was manufactured as described earlier. The ground band, as it became named and thus referred to, was held in place on the upper arm by means of a double sided velcro fastener. Copious amounts of electrode paste were applied to both the inner surface of the band as well as the wiped area of the upper arm to help ensure a good connection. Trials with inadequate amounts of paste or loose application of the velcro fastener resulted in high band impedances and significant noise contamination of the signal. A smaller band was subsequently fashioned after it was found that the larger band could not be made to fit around the slimmer upper arm of female participants without

increased risk of pinching the skin between the ends of the band. The desired impedance was determined to be below 3 kΩ, and preferably below 2.5 kΩ. The presence of a poor ground was recognizable by the presence of 60 Hz noise contamination in the collected waveforms. Figure 31 represents an single frame to illustrate the easily identifiable 60 Hz contamination.

Insert Figure 31 about here

Figure 32 illustrates the resultant effect of 60 Hz noise due to poor ground impedance on the averaged waveform. The 60 Hz noise waveform was evident rendering discrimination of the TSEP impossible.

Insert Figure 32 about here

In monitoring the real-time data collection, the operator could also visually detect the rolling motion of the 60 Hz noise across the screen. The 60 Hz noise typically had a greater amplitude than the TSEP waveform and thus could be visually detected by an experienced observer. The appearance of 60 Hz noise during data collection would be indicative of a poor ground connection. This was borne out through experimental practice, in that once the ground band impedance was rechecked following the data collection in which 60 Hz noise was suspected, often it would be found that the impedance had increased to levels above 3 kΩ. Quite often, this was due to slippage of the ground band due to an insecure fit, or change in the arm-band contact due to participant movement. These scenarios were quite common if proper care had

not been exercised to obtain a proper ground band impedance during the initial hook up. The importance of operator proficiency cannot be underestimated.

Discussion - Cortical recording sites

If there is a section in the present thesis which requires more comparative data, the cortical recording site section would fulfil that requirement. Because of the attention focused on the myriad electronic difficulties, there was no systematic comparison of the various recording sites with the present equipment configuration. The initial recording sites were based on slow-wave cortical EEG methodology, while the latter sites were based on sites localized over the somatosensory cortex.

As has been documented in the existing literature, (Leandri, Parodi, & Favale, 1985; Leandri, Parodi, Zattoni, & Favale, 1987) TSEPs could be recorded from various cranial sites, although the shape of the waveform may exhibit changes in response to the recording sites chosen. Instead of a detailed evaluation of the merits of each potential cortical recording site, it was sufficient for the purposes of the present study to document that TSEPs could be successfully recorded from the somatosensory cortex while using an Fz reference.

The location of the reference and ground electrodes were found to make a significant difference in the recorded signal integrity. While situated on the mastoid, the reference electrode was vulnerable to stimulation artifact being transmitted across the skin. Epidermal tissue, with its natural oils, is known to form an effective conductor, and, as such, may have been aiding the undesired

transmission of the stimulus pulse, contaminating the reference electrode signal with artifact.

The placement of the ground electrode also contributed to TSEP clarity. If the ground electrode was located too close to the recording electrodes, its original function may have been inadvertently defeated through its conduction of errant stimulus artifact or other RFI. Through placement of the ground electrode at a site sufficiently removed from the possibility of stimulus artifact contamination, the TSEP signal clarity improved dramatically. While a detailed examination of the properties of electrical circuits would be beyond the scope of the present thesis, it would be sufficient to demonstrate that accurate grounding of the participant during data collection was advantageous to the final TSEP derivation from the analog microvoltage recorded from the scalp.

Electrode impedances emerged as an area of importance. The EEG standard of impedances below 5 kΩ was untenable for the present study. Cortical electrode impedances had to kept below 2 kΩ, or preferably around 1.5 kΩ for recording of noise-free TSEP data. If the impedances were higher than desired, it would quickly lead to signal degradation, rendering that data set often unusable. In the presented figures there were vertical artifacts in several of the waveforms at time zero. This arithmetic artifact, from averaging of the two polarity pulse data sets together was indicative of the slight difference in the widths of the respective skin artifact pulses, as discussed earlier.

An area of concern arose from the potential overlay of 60 Hz onto the desired data. Given that the desired TSEP had a negativity at 19 msec, one

must be alert to the similiar appearances of the experimental signal versus 60 Hz noise artifact. The presence of 60 Hz noise could be evaluated on two aspects:

i) the strongest indicator of the presence of 60 Hz noise would be the sinusoidal pattern with a periodicity of 16-17 ms, corresponding to the 60 Hz waveform;

ii) the sinusoidal wave pattern itself would also be another strong indicator since TSEP waveforms rarely have the same peak-to-peak amplitude for each of the waveform components, which 60 Hz noise would exhibit. The waveform evaluation was also substantiated by review of other thalamic waveform SEP components, such as median nerve studies published in the literature (Chiappa, 1997).

A deficiency within the present data arose from the lack of TSEP comparison between ipsilateral and contralateral recording or the concurrent recording of TSEPs bilaterally. A natural progression in terms of data collection methodology, especially for the whiplashed subgroup, would have been the comparison of TSEPs bilaterally. Such data may have allowed for comparison of the extent of TSEP alteration in that the exhibited changes occurred only on one side or bilaterally. It would be worthwhile to determine if TSEP alteration would be exhibited bilaterally in cases of forward-facing cervical extension injury. Another important question arises as to the influence of the vehicle occupant's head position, just prior to impact, on the extent of unilateral or bilateral TSEP alteration. These would be but a few areas which merit further

exploration and documentation through additional data collection with both uninjured normals and whiplashed participants.

Issue 4 - Stimulation Electrode Design and Placement Location

A 20 mm circular electrode prototype was initially manufactured from brass metal. The electrode consisted of a five mm diameter center electrode separated from a six mm thick outer electrode by one mm of non-conducting epoxy. The insulating epoxy also provided structural stability to the electrode. The electrode design was based on a suggestion by a fellow graduate student at a recent conference (W. Mueller, personal communication, 1998) based on some preliminary work done on artifact suppression.

This electrode design was quickly abandoned for several reasons: the weight of the brass made it cumbersome when applied to the face and also contributed to the electrode frequently falling off the face; the shape of the electrode made it difficult to apply adequate electrode paste to create sufficient contact with the skin; the close proximity of the two electrode terminals was problematic in that they would often be bridged by electrode paste effectively shorting out the electrode and preventing any stimulation pulse from being conducted. Other than for the initial prototypes, brass was no longer utilized for electrode construction given its propensity for undesirable ionic processes (Durand, 2000).

A smaller version was manufactured to alleviate the weight problem. The smaller electrode was ineffective due to virtually continual bridging between the electrode terminals, rendering it ineffective due to the shorting out of the circuit

by the electrode paste bridge. The small size of the electrode terminals was also questionable as to adequate surface contact between the electrode and the skin to ensure transmission of the stimulus pulse.

For the present study, two 8 mm diameter platinum electrodes were used as the stimulation electrodes. The two stimulation sites employed in the present study were either 'bipolar', i.e., each stimulating electrode was placed approximately 2 cm lateral and 1 cm superior and inferior from the juncture of the *oris obicularis* muscle on the face, or, alternately situated 1 cm medial over the mandibular foramen. Initial trials in the bipolar orientation consisted of electrodes placed 1 cm inferior and superior from the juncture of the *oris obicularis* muscle on the face.

Figure 33 represents one of the initial trials with stimulation by the lip. The presence of the ramping effect, due to filter decay as discussed previously, was evident. The waveform configuration was unexpected when compared to other TSEP waveforms in the literature.

Insert Figure 33 about here

Figure 34 represents one trial, where the stimulating electrodes had to be repositioned because they had fallen off of the face. It was evident that a positioning error had occurred since the recorded waveform was pronouncedly different. The cortical electrode impedances on the trial were also above 3 kΩ but below 5 kΩ, contributing to the noise within the waveform as well.

Insert Figure 34 about here

Figure 35 illustrates the TSEP from a trial using cortical recording from C_{cl} following bipolar stimulation of the lip with 10 mA of stimulation intensity, after the lateral adjustment of electrode position.

Insert Figure 35 about here

Differences between the two polarity waveforms were evident. The positive polarity stimulus pulses produced the expected waveform configuration while the negative polarity pulses produced a somewhat different waveform of more irregular shape. Figure 36 illustrates the average of the two separate pulse trains indicated in Figure 35.

Insert Figure 36 about here

Figure 36 illustrates the potential for a misleading or erroneous overall average waveform to be generated by the simple averaging of two significantly different waveforms. The erroneous distortion arising from the mathematical transfer of irregular peaks from one pulse train to the overall average waveform was evident.

A latency shift was also noted at the N19 peak. On one stimulus pulse average, the maximal negativity occurred at 19 ms, while the parallel maximal negativity in the opposite polarity stimulus pulse average occurred at 20 ms.

The resultant average of the two waveforms created a distorted "V" shape over the maximal negativity. The phase shift was evident in many of the trials in which the bipolar stimulation configuration was utilized. In some unreported trials, the N19 peak had the appearance of an irregular "W" in shape.

Figure 37 illustrates a trial utilizing stimulation over the mandibular foramen. There does not appear to be a predominant latency shift at P19 as noted in the bipolar stimulation configuration. Over the course of 22 different trials involving stimulation over the foramen, the resultant TSEP waveform was generally more defined than those arising from an equal number of trials utilizing bipolar stimulation.

Insert Figure 37 about here

Discussion - Stimulation electrode design and placement location

Although the initial two electrode designs were meant to be prototypes, the continued use of brass was not recommended given the likelihood of metal corrosion through the ionic processes at the skin during transfer of the current pulse (McGill et al, 1982; Durand, 2000). After some discussion, it was decided that standard gold-plated EEG electrodes would also be susceptible to similiar corrosion with prolonged use. It was then suggested to fashion electrodes out of an inert metal, such as platinum, to minimize the risk for tissue damage from ion transfer arising from, in essence, the electrolytic corrosion of the stimulation electrodes.

Based on the existing literature, the preferred stimulation electrode would

have been manufactured from silver/silver chloride (Ag/AgCl) due to its reaction characteristics being similar to a perfectly nonpolarizable electrode (Neuman, 2000). Inadvertently, a highly polarizable metal, namely platinum, had been used to fashion the stimulation electrodes. While the net effect of having used platinum electrodes is presently unknown, a comparison as to the differences between platinum and silver-silver chloride electrodes would be indicated in future research. Since all stimulation was performed utilizing the platinum electrodes, one would assume that any concern arising from the choice of electrode material would be consistent across subjects. Time constraints and the lack of ready availability of Ag/AgCl electrodes in the required size, other than by custom order, also contributed to the continued use of the platinum electrodes.

The anatomical location for the placement of the stimulation electrodes was an important factor in the determination of whether or not TSEP waveforms were recorded. Once the cortical recording site had been changed to C_c, as noted earlier, the recorded TSEP waveforms began to exhibit similarity to previously published TSEP waveforms. It was of considerable concern that only the trigeminal nerve be stimulated in order for the recorded SEP to be of trigeminal origin. The other possibility would have been a mixed SEP arising from a dual stimulation between, for example, the trigeminal nerve and the facial nerve. Such a confound would have proven to be highly problematic to resolve. In the initial trials, as shown in Figure 33, the obtained waveform did not resemble any of the expected waveforms. Interestingly, others had recorded

a similiar waveform and concluded that its origins were undetermined (Drechsler & Neuhauser, 1985). The commonality was the use of a lip stimulation site.

A suggestion had been made to stimulate in the bipolar configuration further away from the lip (B. Stemmler, personal communications, 1999) based on the rationale that stimulation over both the maxillary and mandibular branches of the trigeminal nerve should, at least in theory, increase the likelihood of successfully stimulating the trigeminal nerve. The bipolar stimulation as suggested was attempted for many trials. In the process, numerous obstacles were identified: accurate land-marking was difficult in that facial region due to the absence of definitive anatomical landmarks; adhesion of the electrodes was problematic due to the fact that the adhesive tape would frequently cross over the lips, causing some discomfort for the participants; the curvature of the face in this region made electrode adhesion difficult and electrodes would frequently fall off; accurate placement was critical to avoid artifact from the facial nerve, which was predominant in the area around the lips; as well as muscle twitch artifact from inadvertent stimulation of the afferents to the *oris obicularis* muscles. To adjust for the 'lip effect' of electrodes falling off due to lip movement and incomplete tape adhesion due to facial topography, the bipolar electrode configuration had been changed to two cm from the juncture of the *oris orbicularis* and one cm superior and inferior from the horizontal of the juncture.

Given that the lips are innervated by the facial, or seventh cranial, nerve, it

would be problematic to clearly differentiate which nerve was being stimulated if stimulating around the lips. Given the different waveforms seen in Figures 33 and 34, compared to 35 and 36, there is a stronger argument which can be made for stimulation at an anatomical site which is less susceptible to the confound of dual nerve stimulation. After further review of the facial anatomy (Wilson-Pauwels, Akesson, & Stewart, 1988) as well as the existing publications on trigeminal stimulation (Drechsler & Neuhauser, 1985), note was made of the fact that the mandibular branch of the trigeminal traverses to the ventral aspect of the mandible through the *foramen mentale*. Application of the stimulus over the mandibular foramen had the benefit in that it would localize the stimulus to the mandibular branch of the trigeminal nerve. The foramen also had the advantage of being situated by the second pre-molar in each mandibular quadrant, allowing for ready anatomical land-marking. The mandibular trials consistently produced more robust TSEPs and was thus became the preferred site of stimulation.

The argument against using stimulation near the lip was strengthened by the observation by Buettner, Petruch, Scheglmann, and Stohr (1982) that different branches of the trigeminal were being stimulated in the bipolar configuration. They observed that the mandibular branch of the trigeminal had a slight increase in latency and that comparison of the maxillary and mandibular branches typically produced a distorted "W"-shaped peak at P19 due to the different latencies. Note that due to use of a different nomenclature in which negative is 'up', their peak at 19 ms is labelled positive, hence the P

designation. In the present study, the alternative nomenclature was employed in which positive was 'up' and negative was 'down'. Nonetheless, regardless of the nomenclature employed, it would be the 'same' peak occurring at 19 ms. Given the difficulty with adequate resolution of the early components, the earliest pronounced peak to detect such a differentiation is, by default, the N19. Allison (1982) noted the N19 distortion as being due to it having a broad scalp distribution, which would then be picked up by other scalp electrodes, including F_z. He also noted that the use of a non-cephalic reference may also contribute to the widening of the peak.

As their protocol involved concurrent stimulation of the upper and lower lip, Buettner, Petruch, Scheglmann, and Stohr (1982) also note that a direct motor response of the *oris orbicularis* muscle distorts the latency of the P19 to higher latency values. This would pose a difficult question to resolve, namely whether the slight latency delay was due to the simultaneous stimulation of two different branches of the trigeminal, or was it due to muscle activation of the *oris orbicularis,* and thus of the facial nerve, or a combination of both. Thus, one would lean towards recording over the mandibular foramen as the practical advantages would outweigh the disadvantages.

The trigeminal response was noted as being different for each of the stimulus pulses. At the 10 mA stimulus intensity, one of the pulse polarities tended to exhibit a greater degree of trigeminal response than did the opposite polarity pulse. That type of waveform became somewhat common in the trials, in that one pulse train produced the expected waveform while the other pulse

train did not produce the expected waveform response. To have averaged the two waveforms together would have produced a distorted average which would not have accurately reflected either of the pulse trains. As discussed earlier, the different waveforms arose from different degrees of trigeminal response. It was possible that while one pulse polarity had reached the nerve response threshold, the other opposite polarity pulse may have been at a subthreshold level. Thus, with different stimulus thresholds, the differing degree of trigeminal response would not be surprising.

The increase in the stimulus intensity, to the 12 mA level, increased the trigeminal response sufficiently such that both stimulus pulses exhibited a trigeminal neural response. Such was the interrelated nature of the TSEP study. One issue would lead the way for another separate issue to be addressed, which in turn would lead to a third issue being addressed by the two previous factors in unison.

Preliminary Participant Results

The main focus of the present thesis had been directed toward the methodological development of a reliable and reproducible non-invasive measure for TSEPs. Once the present TSEP recording was both reliable and reproducible, the collection of pilot data included the evaluation of trials from both uninjured and whiplashed participants.

Trials on uninjured participants

Since the data collection was still in the pilot stage, data were collected from participants using both the bipolar and mandibular configurations. As long

as the impedances, as discussed earlier, were controlled to fall within the specified parameters, the data were generally useful when recorded over a 50 ms epoch.

Insert Figure 38 about here

Figure 38 illustrates the mandibular averages from four normal subjects. As can be seen, the waveforms were reasonably replicable across subjects. The N19 peaks were distinct, while the rise to P27 were less defined across the waveforms. The appearance of peaks at P13 were of interest, although they tended to be somewhat masked by the negativity leading to N19.

Trials on whiplashed participants

Over the course of data collection, four individuals were identified who had previously experienced a flexion-extension injury of the cervical spine. Two subjects initially identified having experienced a cervical injury, although any trigeminal involvement was unknown. As can often be the case in research, it so happened that two uninjured participants became members of the injured subgroup. Their memories were 'refreshed' in that following review of the obtained waveforms and in response to further questioning, accidents previously forgotten or deemed as not relevant were identified. The whiplashed group mandibular waveforms are presented in Figure 39.

Insert Figure 39 about here

Several differences were noted in comparison to the uninjured waveform

profile discussed earlier. The flatness of the injured group waveforms were evident, especially in terms of the P13, N19, and P27 peak-to-peak amplitudes. These findings were considered to be replicable, as three of the four participants had been tested on two different occasions, with similiar results during each session.

Figure 40 superimposes the average of 4 non-injured participants over the average of the 4 whiplashed participants. The difference between the N19 peaks was notable, as was the flattening of the P27 peak. There was no noticeable P13 peak in the injured waveforms.

Insert Figure 40 about here

Particularly noteworthy was the fact that all four 'injured' participants reported ongoing physical symptomology. One participant was involved in a hockey injury in which they were "violently slammed" into the sideboards while playing hockey. Since that injury, they reported having lost part of their ability to smell but had not had the anosmia medically tested. Another participant reported having been broad-sided in an intersection 8 years ago, striking their head on the driver's side door, and was still dealing with "post-traumatic headache". The third participant reported having a problem with "fairly bad headaches" for which they had sought medical intervention. Diagnostic imaging had apparently not found any pathological cause for the headaches. When questioned further, that participant denied any sport or automobile accidents. They did report having fallen down a steep flight of stairs while in the

primary grades of elementary school. The participant did recall that medical intervention had been sought at that time. The fourth participant reported having been involved in a motor vehicle accident three years ago in which they were "rear-ended by a (literal) Mack truck". They reported a headache history but chose not to elaborate further. When specifically asked, all participants denied the occurrence of any additional trauma since the headache-related injury.

Given the limited number of trials in each group, there were limited statistical analyses which could be performed on the available data. Table 3 summarizes the peak amplitudes for the 4 subjects in each group for the P13, N19, P27 peaks and their differentials. Examination of latencies was not feasible due to the limited number of individuals in each subgroup.

Insert Table 3 about here

Table 4 presents the results of a one-way ANOVA between peak amplitudes between the two groups. It was noteworthy that the N19 peak amplitude difference was statistically significant between the two groups, as were the P13-N19 and N19-P27 peak-to-peak amplitude differences. The difference in P13 amplitude between the two groups approached a statistically-significant level. Further statistical analyses were not feasible given the small number of participants in each group.

Insert Table 4 about here

During the earlier referenced trials over a 100 ms recording epoch, a

fortuitous observation was made. Due to the equipment limitations discussed earlier, use of a 100 ms recording epoch necessitated the use of a 100 µs stimulus pulse width. It was observed that, while being stimulated with the higher intensity stimulus, whiplashed participants began to produce TSEP waveforms which resembled the TSEP waveform pattern of normal uninjured participants, although still reduced in amplitude. The observation was evident and replicable in three out of four whiplashed participants who were able to be re-tested. The remaining subject was unable to be re-tested. Figure 41 illustrates a whiplashed TSEP produced by the normal 50 µs pulse width superimposed on a whiplashed TSEP produced by a 100 µs pulse width.

Insert Figure 41 about here

Discussion - Preliminary participant results.

Intriguing experimental results were presented in Figures 38-40. In Figure 38, the mandibular waveforms from uninjured participants were superimposed, illustrating a pronounced degree of uniformity. When compared to the 'injured' profiles, pronounced differences between the averaged waveforms were evident, as illustrated in Figure 40. With the injured profiles, the waveforms were fairly symmetrical with each other, albeit to a somewhat lesser degree than the 'normal' profiles.

In the 'whiplashed' profiles, there was a statistically significant decrease in the amplitude of the P19 waveform component along with a flattening of the peak of the N27 waveform component. These observations lend support to one

of the experimental hypotheses, namely the expectation of decreased amplitude in TSEPs of whiplashed individuals. Although one cannot draw any definitive conclusions on the basis of only 4 profiles, the preliminary validation does justify further experimental investigation of the decreased TSEP phenomena in whiplashed participants.

Highly intriguing was the concurrent incidence of all four of the 'whiplashed' participants reporting having both experienced an accidental injury involving their cervical spine and the presence of ongoing physical symptoms in the present. The age of injuries ranged considerably, from a injury 20 years ago (in childhood) to as recent as three years ago. Three main factors, nonetheless, emerged: i) all had been involved in accidents involving flexion-extension or rotation of the cervical spine; ii) all reported ongoing physical symptomology since that time; and iii) their respective waveforms all indicated decreased amplitudes for the predominant TSEP waveform components.

Even more intriguing were the results illustrated in Figure 41. For individuals within the 'whiplashed' group, their TSEPs were noted to begin exhibiting increased amplitude in the N19/P27 component peaks in response to a stronger stimulus. An increase in the pulse width from 50 μs to 100 μs essentially doubled the stimulus being delivered to the trigeminal nerve. In whiplashed individuals, under baseline stimulus conditions, to which uninjured participants produced notable TSEPs components, injured participants produced TSEPs components which were 'flatter' than those produced by the

uninjured group. In response to an increased stimulus, the injured group was able to begin producing a TSEP of increased amplitude. The presence of a TSEP to the increased stimulus helped rule out operator or experimental error being responsible for the absent waveform. If either confound was responsible for the flat-line TSEP waveform, an increased stimulus would not have corrected the error and no TSEP should have been recorded. The fact that a TSEP was recorded at the higher stimulus intensity lends support to the argument that it was a genuine TSEP being recorded. Subsequent retesting of the individuals, with similiar results being obtained during the repeat testing a few days or weeks later, served to strengthen the argument for a valid TSEP recording and not one produced by experimental error. It would also suggest that the altered TSEP was a reliable phenomenon, being replicable over time.

Given these observations, one could begin to postulate some exciting scenarios as to trigeminal neural conduction after whiplash injury. It may be possible that the trigeminal pathway of whiplashed individuals, while still capable of conducting neural transmission, requires a greater stimulus intensity, greater than that required by non-injured individuals to produce a similiar level of thalamic response to the stimulus. There are numerous possibilities to explore experimentally, especially in light of the findings that ascending brainstem pathways have been linked to the activation of other thalamocortical systems (Steriade, 1999). The scenario of reduced neural input reaching the thalamus due to neural damage, and accordingly being reflected upstream to higher brain centres en route to the somatosensory cortex would

be alluring. Although these possibilities still need to be borne out experimentally, they may perhaps be the initial stages of some exciting refinements in the current model of inhibitory control mechanisms in chronic pain.

Given that these phenomena were not explored further in this thesis, the true significance remains to be addressed through further research. Notwithstanding, the present experimental findings would justify further investigation of altered TSEPs in whiplash. If the preliminary findings were borne out by additional confirmatory data, it may have further benefit, not only as a possible diagnostic test for whiplash injury, but also by having an impact on present models of cortical processing of chronic pain (Kanda et al, 2000).

General Discussion

In the present thesis, both hypotheses were substantiated, indirectly lending support to the proposed model for whiplash injury. The non-invasive surface recording of TSEPs was demonstrated to be feasible, albeit through the resolution of a number of technical issues. The preliminary participant results lend support to the second hypothesis through the recording of significantly different TSEP waveforms. Whiplashed participants were seen to have decreased amplitude in several key waveform components when compared to uninjured participants. Given the limited number of participants, further exploration of the noted TSEP waveform observations would be merited to further document the initial findings presented herein.

Data integrity - artifact and contamination

Undoubtedly, one of the largest challenges in the non-invasive surface recording of TSEPs was the presence of stimulation artifact. Since both the stimulation and recording electrodes were located close to each other, separated by mere centimeters, the stimulation artifact would be easily detected by the recording electrodes. Since the TENS stimulus artifact, in all likelihood, was conducted across the skin, there was little which could have been done to prevent the artifact from reaching the recording electrodes. Once it reached the recording electrodes, the predominant sequelae would be significant contamination of the scalp EEG recording through the creation of electronic artifact by overloading either the amplifiers or in-line filters.

The artifact magnitude was so immense, compared to the TSEP amplitude, that it would have easily saturated the electronics. This would have increased both the degree of signal distortion as well as the time requirement for the electronics return to baseline. The railing of the DSP, evident through the off-scale square wave appearance of the early artifact, confirmed the impact of the stimulus artifact. The clipped signal then decayed into an alternating wave of decreasing amplitude, due to amplifier ring, slowly returning to baseline. In unreported observations, the stimulus artifact was measured to be in excess of 300 μV in amplitude. Since the desired TSEP magnitude was in the 1-2 μV range, the problem was evident. If the electronics were designed to detect a 1-2 μV signal, then it is not surprising for the electronics to be overwhelmed by a 300 μV artifact. Conversely, if the electronics were designed to withstand a 300

μV artifact, resolution of a 1-2 μV signal would be highly unlikely, especially in the 20-30 ms event time frame for a TSEP.

The effects of stimulus artifact may be even more pervasive than initially thought. One of the early TSEP studies (Leandri, Parodi, & Favale, 1985) published, as their findings, signal patterns reminiscent of the present findings of amplifier ringing. Without ascertaining the technical details as to the amplifiers and filters employed in the Leandri et al (1985) paper, one could not state definitively that indeed they were measuring artifact rather than true TSEP waveform, nor could one with confidence support the reverse argument either. On closer review of their results, an argument could be made against the validity of that data, in that their waveforms were comparable to those reported by others as amplifier artifact (McGill et al, 1982). The results from the present study would support the comparison to amplifier artifact as well.

The filter response presented a truly monumental challenge, since conventional EEG methodology routinely utilizes in-line band pass filtering in the amplifiers. A number of different filter configurations and frequency ranges were attempted during the equipment debugging, nonetheless the artifact was of such magnitude that it would consistently rail the filters. The artifact would even rail a conventional notch filter for 60 Hz noise. The filters would eventually recover as designed and return to baseline. Unfortunately, the time required for them to do so, within the millisecond domain, was sufficiently long to prevent the recording of any useful data during the first 10-15 ms post-stimulus. Under many ordinary uses in electronics, a recovery window of 10-15 ms would not be

uncommon nor would it be problematic. However, with the focus of the present study, such a time delay spanned the time epoch of interest, preventing the recording of any useful data during the desired time frame. Since one of the initial hypotheses of the present thesis involved the recording of early TSEP components, the presence and sequelae of the artifact proved insurmountable for that possibility.

Of critical importance was the time period it took for the electronic amplifiers to recover or return to their operational baseline. Once the amplifiers had returned to baseline, the ensuing data theoretically should have been less contaminated by such artifact. The risk for contamination or signal degradation did remain, to some degree, a possibility unless the amplifier response had been fully documented through significant testing (Bronzino, 2000). The use of a faster recovery broad-band amplifier integrated circuit in the pre-amplifier pod did provide a decrease in the degree of residual amplifier artifact. Regrettably, by itself, it was not sufficient to overcome the stimulus artifact problem.

The removal of the in-line filtering in turn presented significant challenges due to the contamination of the signal by spurious unwanted RFI. The presence of low frequency contamination proved to be problematic. The largest contamination arose from 60 Hz electrical noise. As discussed earlier, 60 Hz noise was abundant, even within the sheltered confines of the ERP laboratory. Given that it was the electrical line frequency, the pervasiveness of the problem was not overly surprising given the sheer abundance of electrically powered devices, both within and around the lab. Further high frequency RFI pollution

was also a concern given the use of the adjacent Schmon tower as a base for various broadcast antennae.

Sometimes the simplest solutions were the most effective. Simple arithmetic averaging was often helpful in removing a fair amount of noise from the data. In unreported trials, spurious artifacts could be seen rolling across the screen during data collection, yet were absent in the final average. The example serves to demonstrate the advantage of cumulative averaging, such that spurious artifact were removed simply through the process of averaging rather than elaborate filtering schemes. If a certain frequency noise was present, it should in theory be present at a different point in time during each stimulus pulse given the stimulus parameters. When several hundred stimuli were averaged together, the noise would appear to be essentially random and would be averaged out.

Since the data were averaged over a significant number of trials, the continued presence of specific frequencies of noise in the averaged waveform was surprising. As an example, the continued presence of 60 Hz or slow wave contamination would suggest that they were time-locked in some way, thus allowing their effect to be evident in the averaged waveform. Their continued presence would be problematic and would necessitate further investigation as to its origins and utilization of methods to prevent its continued impact on the recording system.

Even though RFI contamination was present in the data, there were practical limits as to its removal. The use of a rolling-window average was

beneficial but was limited, as demonstrated earlier, in its capacity to completely remove noise. Given the small number of usable trials in the present study, they were simply insufficient upon which to base any advanced post hoc digital filtering attempts. Similarly, the scope and development of such filtering parameters may have significantly added to the time and resource commitment to the present thesis. It was sufficient to demonstrate that one 'was on the right track', thus justifying further exploration of the trigeminal phenomena and the issues pertaining to its measurement which would then need to be addressed in due course.

One concern which clearly merits further exploration was the degree of 60 Hz contamination of the TSEP waveform. Given its prevalence in and around the recording lab, its presence or absence cannot be summarily dismissed nor simply acknowledged. One has to contend with not only with the 60 Hz contamination but also with the related harmonics. A significant obstacle was the undesirable overlap between the 60 Hz noise waveform characteristics and those of the TSEP waveform. Given that the stimulus artifact typically lasted for 2-3 ms, and based on the periodicity of 16.67 ms for 60 Hz, it would place the 60 Hz noise in close proximity, if not superimposed on top of, the N19 thalamic negativity. If this were to be the case, then the TSEP would be highly contaminated and could not be used for any meaningful interpretation. While the presence of 60 Hz was evident in the waveforms resulting from trials in which there was a poor ground connection, a strong argument can be made for its absence, or at least a minimized effect, in those trials with carefully

controlled impedances.

A strong argument can also be made from examination of the waveforms from the whiplashed subgroup. Should 60 Hz contamination be problematic across all waveforms, then one would expect to see the tell-tale sinusoidal wave present in those waveforms as well. The absence of the sinusoidal waveform would attest to the cleanliness and subsequent validity of the data. Since the same equipment and procedures were used to collect the data from both groups, it also strengthens the argument that, once proper measures were employed, the presence of 60 Hz contamination could be minimized. The presence within the data of numerous trials contaminated with 60 Hz noise also confirms the need to carefully follow experimental protocol.

A related argument to strengthen the validity of the present data would be the similarity of waveform patterns, albeit with different latencies, between scalp recordings of median nerve SEPs (Ganes, 1980; Chiappa, 1997), cortical recordings of median nerve SEPs (Allison, 1982; Dinner, Luders, Lesser, & Morris, 1987), both scalp and cortical recordings of median nerve SEPs (Katayama & Tsubowkawa, 1987), intracortical recording of trigeminal SEPs (Ridderheim, Von Essen, Blom, & Zetterlund, 1985), and scalp recording of trigeminal SEPs referred to earlier. The strongest argument would come from the intracortical recording of median SEPs during a surgical procedure (Hashimoto, 1984). Since the waveforms documented in those references were in agreement with each other, as well as to those in the present study, one may take some assurance that one indeed had reliably recorded

trigeminal SEPs from the scalp.

The need for real-time current measurement became evident with the observation that the skin-electrode impedance generally increases during the experimental session because the electrode paste is depleted of charge conducting ions (McGill et al, 1982). In the absence of any current measurement capability, variations in current intensity during the experiment would be missed by the experimenters but would likely have an effect on the experimental results.

The skin-electrode interface has been speculated as being a complicated interactive milieu (McGill et al, 1982) between the skin, namely the keratinous layer and the epidermis which form a resistive sheath around the connective tissues contained therein. It has been noted previously that the anode voltage is larger than the cathode voltage due to intrinsic differences in skin impedance (McGill et al, 1982). They have also noted that, after a constant-current pulse, the skin capacitance discharges through the skin resistance, requiring a period of time to do so. Such time period has yet to be accurately quantified in published research studies, although the response properties of specific types of cells have been modelled (Foster, 2000; Varghese, 2000). The capacitive effect of the skin has also been noted as being approximately 0.03 μF (McGill et al, 1982). Although the capacitance of skin was noted as being constant regardless of the skin preparation prior to electrode application, it does vary depending on the surface area of the skin in contact with the stimulating electrode (McGill et al, 1982). Both of these factors would play an

important role in the overall skin-electrode stimulation dynamic and should be kept under consideration.

One consideration which has not been discussed in previous trigeminal SEP publications involves the stimulation electrodes half-cell potential or the galvanic skin response thereto. The interaction of the skin, the electrolytic electrode paste, and the stimulating electrodes all interact to create a localized electrical phenomena. McGill et al (1982) outline that

> "metal atoms dissociate into the electrolyte and form a double-charge layer which is responsible for the DC half-cell potential, the large electrolytic capacitance between metal and solution, and the parallel frequency- and current-density-dependent polarization capacitance. Direct current crosses the interface via electrochemical reactions in which electrons in the metal are exchanged for ions in solution, and the resulting voltage drop is non-linearly related to the current" (pg. 130).

Thus, the electrochemical interaction at the electrode-skin junction, which often is overlooked, is important since it, in and of itself, can influence the dynamics of the current delivery across those electrodes. Again, what the experimenter thinks is being applied to stimulate the nerve may not in fact be the case due to this localized response. McGill et al (1982) point out that, for a pair of 1 cm diameter stainless steel electrodes, the half-cell potential effect "is typically several-tenths of a volt, the net capacitance is about 50 μF, and the effective resistance is several kΩ" (pg. 130). This is not an insignificant capacitance and its effect in the stimulation circuit cannot be ignored.

A related consideration would be the polarizability of the electrode material. In the present study, platinum was used to manufacture the electrode terminal with the intension of minimizing the likelihood of ion transfer into the

participant's skin. However, the highly polarizable characteristic of platinum may have had an effect on stimulation since polarizable electrodes change the charge distribution within the electrolytic solution [sic electrode paste] and no actual current passes crosses the electrode-electrolyte interface (Neuman, 2000). The question of the loss of stimulus intensity, if any, would need to be addressed if the use of polarizable electrodes were to continue. Given that the other experimental variables were kept constant, the presence of a polarizable electrode may have served to introduce a uniform confound across all trials in the present study.

The obvious question arises as to available means to control the artifact. Bennett and Jannetta (1980) suggested stimulation of the gums rather than transcutaneous stimulation of the trigeminal nerve. Other authors (McGill et al, 1982) have suggested blocking the first few ms of signal from reaching the amplifiers in an attempt to prevent amplifier saturation, possibly involve the usage of a fast-acting analog switch, which in and of itself would probably create an electrical artifact. Dowman and Stockbridge (1988) have suggested the use of a programmable rapid roll-off low pass filter to block the stimulus artifact. Even then, there is still the possibility of data loss during the blocked interval (Parsa, Parker, & Scott, 1998). Babb et al (1978) suggested the use of fast-recovery amplifiers to minimize the effects of amplifier saturation. Emerson, Sgro and Stanton (1988) suggest the post hoc removal of amplifier saturation artifact. There are many possibilities which would need to be explored.

Hardware - present limitations and future improvements

The presence of the stimulus artifact versus the need for band-pass filtering to prevent spurious noise contamination becomes a vicious circle of cause and effect, one still needing a workable solution. Instead of trying to, literally, deny the obvious, McGill et al (1982) outlined several intriguing possibilities to deal with the artifact. They outline several dual channel recording configurations to allow for the subtractive processing of the artifact from the desired signal. Unfortunately, the implementation of any of their suggestions in the present study would have necessitated major revisions of both hardware and software. The existing DSP board allowed for recording from only one channel. The other hardware components could have been modified to accept two input channels. The data acquisition software would have needed to be completely rewritten since it had been designed and written only for single channel use.

One improvement which could have been easily implemented within the present configuration would have been the continuous recording of the successive testing sessions instead of being limited to a specific recording epoch. Within the data, the onset of the stimulus could be easily detected, allowing for the subsequent post hoc extraction and processing of the TSEP data. Through adjustment of the interstimulus interval, one could indirectly control the length of the single-session epoch, allowing for the recording of the longer latency post-thalamic cortical responses to trigeminal stimulation. An added benefit of such an approach may emerge through the longer data

frames making post hoc digital filtering of slow frequency contamination easier, since the contaminating waveform could be evaluated more easily than it could in short discontinuous fragments.

The possibilities for the future also highlight some of the problems in the present. Several of these issue focus around the hardware and software utilized by the present study. The A2D DSP board, while having the added benefit of higher resolution, was limited by its programming. The programming was limited, not only in terms of the single recording channel, but more so in the ability to control the stimulus pulse width as a fraction of the recording epoch length. This factor was not initially a significant concern but became highly problematic towards the end of the present study. To modify these parameters would have necessitated a complete rewrite of the software. Additional time would have also been required to adequately debug the software prior to its use in the lab for data acquisition.

A related concern deals with the 'patch-work' nature of the existing software code. Considering that it was originally written to perform single-cell recordings from crayfish, its modification to human TSEP recording became a significant undertaking. Frequently, errors were discovered in the 'older' parts of the code which affected the present TSEP collection. A period of time for software debugging, instead of real-time debugging at the cost of real data, would have been highly desirable.

The capacity to record from more than one channel would have been a welcome addition to the present hardware. The use of only one channel is not

in accord with accepted SEP recording parameters, as outlined in Chiappa (1997). Single channel data also made comparisons extremely difficult. For example, it would have been much easier to select the ideal recording site had one been able to compare four or five adjacent recording sites instead of having to collect four or five separate trials to obtain the same data. The ability to determine the broadband distribution of waveform components (Van Nechel, Deltenre, Strul, & Capon, 1982), or even noise distributions, would have been welcome additions.

Additional recording channels would have also been helpful to address some of the 'nagging' questions. Had there been capacity for additional real-time recording, one could have recorded real-time EMG activity from the *oris orbicularis* instead of merely speculating about its existence as a potential confound. Similarly, the real-time monitoring of either the blink reflex or jaw-jerk reaction would have been immensely helpful in addressing concerns as to potential experimental confounds and/or signal contamination. Although it would be an immense undertaking, the present hardware/software configuration would require significant revision to be truly useful for future TSEP data collection.

Another area of improvement for the present system, both in terms of utility as well as susceptibility to 60 Hz noise, would be to repackage the amplifiers into a self-contained battery-operated device. The components being utilized from the main amplifier for the TSEP work, as well as from the pre-amplifier pod, could be easily re-packaged into a smaller, more contained

package. Not only would this eliminate the connection of the system to AC power and close possible noise pathways, it would also eliminate several long cumbersome cables, which in and of themselves have a undesired tendency of functioning as an antenna for RFI. This reinforces the possible gains to be made by re-evaluating the hardware configuration used for the present study.

Implications for future research

The experimental findings of the present study are exciting. Although they are preliminary findings, due to their limited number, they may be the first demonstrable evidence as to neurological impairment following whiplash injury. The utility of SEPs as an indicator of neurological impairments, such as cervical spondylosis and multiple sclerosis, has been addressed previously (Ganes, 1980; Chiappa, 1997). TSEPs have also been used as indicators of lesions within the trigeminal pathology (Buettner, Petruch, Scheglmann, & Stohr, 1982) and even of trigeminal nerve damage following oral surgery (Barker, Bennett, & Wastell, 1987). While the utility of TSEPs as an indicator of neural conduction disruption following injury has not been definitively demonstrated in the literature thus far, the present study may be the first small step in such demonstration.

Even more intriguing was the observation of an increased TSEP in whiplashed individuals as a response to increased stimulation. While it is known that increased stimulus intensity leads to an increased SEP (Leandri, Parodi, & Favale, 1985), the present observation of a 'sub-normal' threshold approaching a 'normal' threshold has not been referred to in the previous

literature.

Given the link between trigeminal function and orofacial pain syndromes, such as temporomandibular joint dysfunction or myofascial pain syndromes, as well as its involvement in migraine etiology (Okesen, 1991; McCall, 1997; May, Buchel, Bahra, Goadsby, & Frackowiak, 1999), the efficacy of trigeminal transmission becomes an important consideration. Sessle (1997) summarizes the findings in murine systems such that

> "alterations in the efficacy of the descending modulatory influences [sic central neural pathways and mechanisms involved in descending modulatory influences on brainstem nociceptive transmission] must also be considered as factors that may contribute to changes... as a result of injury to or inflammation of deep as well as superficial craniofacial tissues (pg. 413)."

Hu et al (1997) expanded on their work with mustard oil irritation in a murine model

> "while damage or inflammation of deep craniofacial tissues such as the temporomandibular joint (TMJ) and masticatory muscles, as well as abnormal muscular activity, are often considered important in the pathophysiology of temporomandibular disorders (TMDs) are related craniofacial pain conditions... Recent findings point to a crucial role played by the subnucleus caudalis of the brain stem trigeminal spinal tract nucleus in the relay and modulation of nociceptive input from deep craniofacial tissues (pg. 497)."

While the observation is, at present, just an observation, it certainly merits further experimental scrutiny and characterization. Since the amplitude of the signal reaching the thalamus was decreased, in comparison to normal subjects, and since the primary relay for the facial stimuli was most likely through the subnucleus caudalis, the possibilities for future research unfold dramatically. The need for future data collection is apparent, and the present

findings serve to justify further research in this area.

The present observations are strengthened by recent experimental findings. Keidel et al (2001) demonstrated, in a total of 82 whiplashed individuals, significant alteration in the regulation of temporalis muscle contraction as measured by EMG. The latencies and duration of the exteroceptive suppressive temporalis reflex were noted by delayed onset and shorter duration. The dysregulation of the inhibitory temporalis reflex in those whiplashed individuals experiencing posttraumatic headache was attributed to a transient dysfunction of a brainstem-mediated reflex circuit following whiplash (Keidel et al, 2001). Further research is clearly merited to elucidate the role of brainstem involvement in post-whiplash sequelae.

The nature of the trigeminal response to the stimulus needs to explored further and documented. Given many factors at the skin-electrode interface, one would need to ascertain the efficacy of stimulation. One would also need to determine exactly what was being stimulated (Wood &.Allison, 1981). One hoped that the trigeminal response was primary, but that would need to be documented. A related issue would be exploring the extent of trigeminal nerve activation. As the trigeminal contains at least two nerve fibre types, it would be prudent to ascertain which fibre bundle was being activated at which stimulus threshold. The effect of activation of both the A-delta and C fibres, given the different conduction latencies for each, would need to be documented as well.

Given the reported decrease in trigeminal response to TENS in whiplashed individuals, it would be advantageous to compare the trigeminal

response to different types of stimuli. For example, one could compare the trigeminal response to tactile stimulation with the response to TENS in terms of thalamocortical processing. Different stimulation modalities would help piece together the present jigsaw of trigeminal response.

Should the electrical stimulation of the trigeminal nerve remain problematic, one could explore other stimulation possibilities. The trigeminal nerve has previously been stimulated by means of chemosensory or olfactory stimuli (Hummel & Kobal, 1992; Hummel, Livermore, Hummel, & Kobal, 1992). Chen and Bromm (1995) made use of a $C0_2$ laser to stimulate the upper division of the trigeminal nerve for their dipole mapping study, while others have utilized laser stimulation in pain studies (Beydown, Morrow, & Casey, 1997). The waveform components resulting from laser stimulation of the trigeminal would be different from those achieved with electrical stimulation. Nonetheless, if the nerve conduction is impaired, that should be reflected regardless of the mode of stimulation.

More importantly, one could explore a realm of possibilities with respect to digital filtering as well as new directions for data analysis. Numerous publications highlight the use of advanced signal processing techniques (Van Boxtel, 1998) , such as fast Fournier transformations, to evaluate the frequency constituents of the EEG signal. Braun, Hanley, and Thakor (1996) outline the use of time-frequency analysis to detect both temporal and spectral changes in SEP waveforms due to injury. A number of authors have posited that subtle changes in the SEP, thus rich in information, would be overlooked with only

superficial examination of SEP data or by averaging SEPs together to produce averaged SEPs (Braun, Hanley, & Thakor, 1996; Robinson, 1999). Likewise, for any meaningful comparisons to be possible between groups, there needs to be a clearer understanding of intersubject variability in terms of SEP waveform component latencies. Sonoo, Kobayashi, Genba-Shimizu, Mannen, and Shimizu (1996) outline a detailed statistical analysis for the selection of parameters and the establishment of normal values. This would be quite important, since SEP abnormalities are usually determined by the absence or presence of specific waveform components or their statistical deviation from mean values (Chiappa, 1997).

In summary, the surface recording of trigeminal SEPs has been a technical challenge on many domains. More importantly, those challenges could be addressed to allow the progression to the non-invasive recording of replicable trigeminal SEPs. The preliminary findings of differences in the trigeminal somatosensory evoked potentials, between uninjured and whiplashed participants, are exciting due to their possible clinical significance. While there is still much research to be done, hopefully the present study has been but a first step along that road. Hopefully, down that road, whiplash patients may continue to be told that 'it is all in your head', albeit at a lower level anatomically than is referred to at present.

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Tables

Table 1

The Cranial Nerves and their Function

Nerve	Number	Function	Modality
Olfactory	I	Sense of smell	Special Sensory
Optic	II	Vision	Special Sensory
Oculomotor	III	Motor to all extrocular muscles except superior oblique and lateral rectus.	Somatic motor
		Parasympathetic supply to ciliary and pupillary contractor muscles.	Viseral Motor
Trochlear	IV	Motor to superior oblique	Somatic Motor
Trigeminal	V	Sensory from surface of head and neck, sinuses, meninges, and tympanic membrane (external surface).	General Sensory
		Motor to muscles of mastication.	Branchial Motor

Table 1 (Cont).

Nerve	Number	Function	Modality
Abducens	VI	Motor to lateral rectus muscle.	Somatic Motor
Facial	VII	Taste, anterior two-thirds of tongue	Special Sensory
		General sensation from a small area around the external ear, tympanic membrane (external surface).	General Sensory
		Parasympathetic supply to all glands of the head except the paratoid and integumentary glands.	Visceral Motor
		Motor to muscles of facial expression, stapedius.	Branchial Motor
Vestibulo-cochlear	VIII	Balance	Special Sensory
		Hearing	Special Sensory

Table 1 (Cont).

Nerve	Number	Function	Modality
Glossopharyngeal	IX	Taste, posterior one-third of tongue.	Special Sensory
		General sensation from posterior one-third of the tongue and internal surface of the tympanic membrane.	General Sensory
		Visceral sensory from the carotid body.	Visceral Sensory
		Parasympathetic supply to parotid gland.	Visceral Motor
		Motor to stylopharyngeus muscle.	Branchial Motor
Vagus	X	General sensation from a small area around the external ear.	General Sensory
		Visceral sensory from pharynx, larynx, and viscera.	Visceral Sensory

Table 1 (Cont).

Nerve	Number	Function	Modality
Vagus	X	Parasympathetic supply to all thoracic and abdominal viscera as far caudal as the splenic flexure.	Visceral Motor
		Motor to pharynx and larynx.	Branchial Motor
Accessory	XI	Motor to sternomastoid and trapezius muscle.	Branchial Motor
Hypoglossal	XII	Motor to intrinsic and extrinsic muscles of the tongue except palatoglossus.	Somatic Motor

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Note: From Cranial nerves: Anatomy and clinical comments (page xiii) by L. Wilson-Pauwels, E.J. Akesson, and P.A. Stewart, 1988, Philadelphia, PA: B.C. Decker, Inc. Copyright 1988 by L. Wilson-Pauwels, Adapted with permission.

Table 2

Constant Current Stimulator Calibration

Dial Setting	Measured mA current output
0.0	1.75
1.0	1.8
2.0	2.1
3.0	2.4
4.0	2.8
5.0	3.4
6.0	4.2
7.0	5.5
8.0	8.5
8.2	9.0
8.4	9.4
8.6	10.0
8.8	13.5
9.0	16.0
10.0	47.5

Note: Current output measured in real-time using a Tektronix Model 6042 current probe and a Tektronix Model 22 portable digital oscilloscope. Refer to the text for further description

Table 3

TSEP Waveform Component Peak Amplitudes

Group	P13	N19	P27	P13-N19	N19-P27
1	0.65	-3.30	0.63	3.95	3.93
1	1.49	-2.38	0.39	3.87	2.77
1	3.13	-3.69	2.14	6.82	5.83
1	1.07	-3.72	1.41	4.79	5.13
2	-0.41	-1.24	-0.09	0.83	1.15
2	0.04	-0.77	0.88	0.81	1.65
2	0.89	-1.38	0.56	2.27	1.94
2	0.28	-0.66	-0.53	0.94	0.13

Note:

1. Group 1 - Uninjured; Group 2 - Whiplash.
2. Amplitudes presenting in uV.
3. P13-N19 and N19-P27 differences presented as absolute values.

Table 4

TSEP Waveform Component Peak Amplitude ANOVA

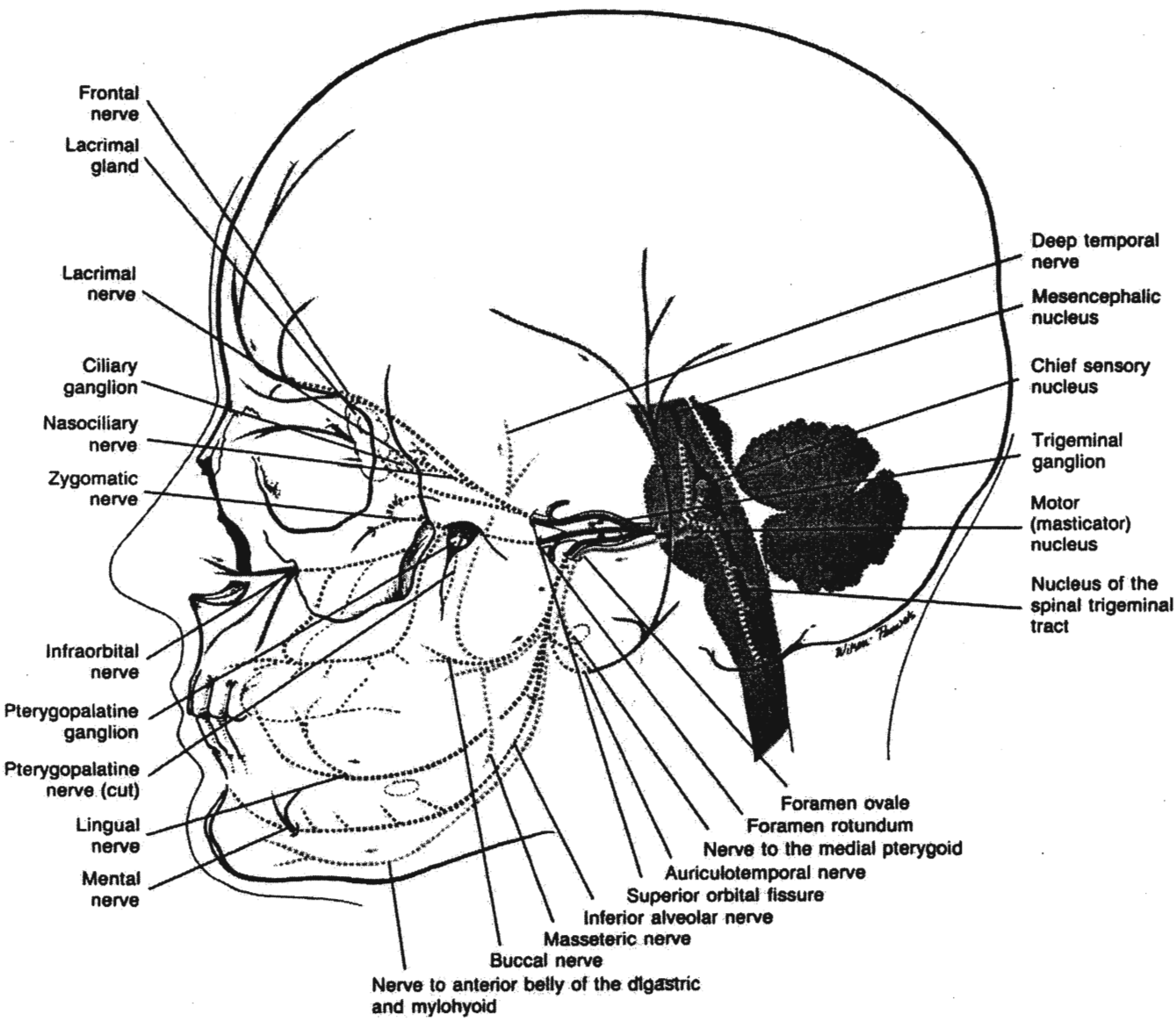
ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
P13	Between Groups	3.836	1	3.836	5.213	.063
	Within Groups	4.416	6	.736		
	Total	8.252	7			
N19	Between Groups	10.215	1	10.215	39.754	.001
	Within Groups	1.542	6	.257		
	Total	11.757	7			
P27	Between Groups	1.758	1	1.758	3.397	.115
	Within Groups	3.104	6	.517		
	Total	4.862	7			
p13N19 amplitude difference	Between Groups	26.572	1	26.572	22.281	.003
	Within Groups	7.156	6	1.193		
	Total	33.728	7			
N19-P27 amplitude difference	Between Groups	20.448	1	20.448	16.690	.006
	Within Groups	7.351	6	1.225		
	Total	27.799	7			

Figures

Figure 1.

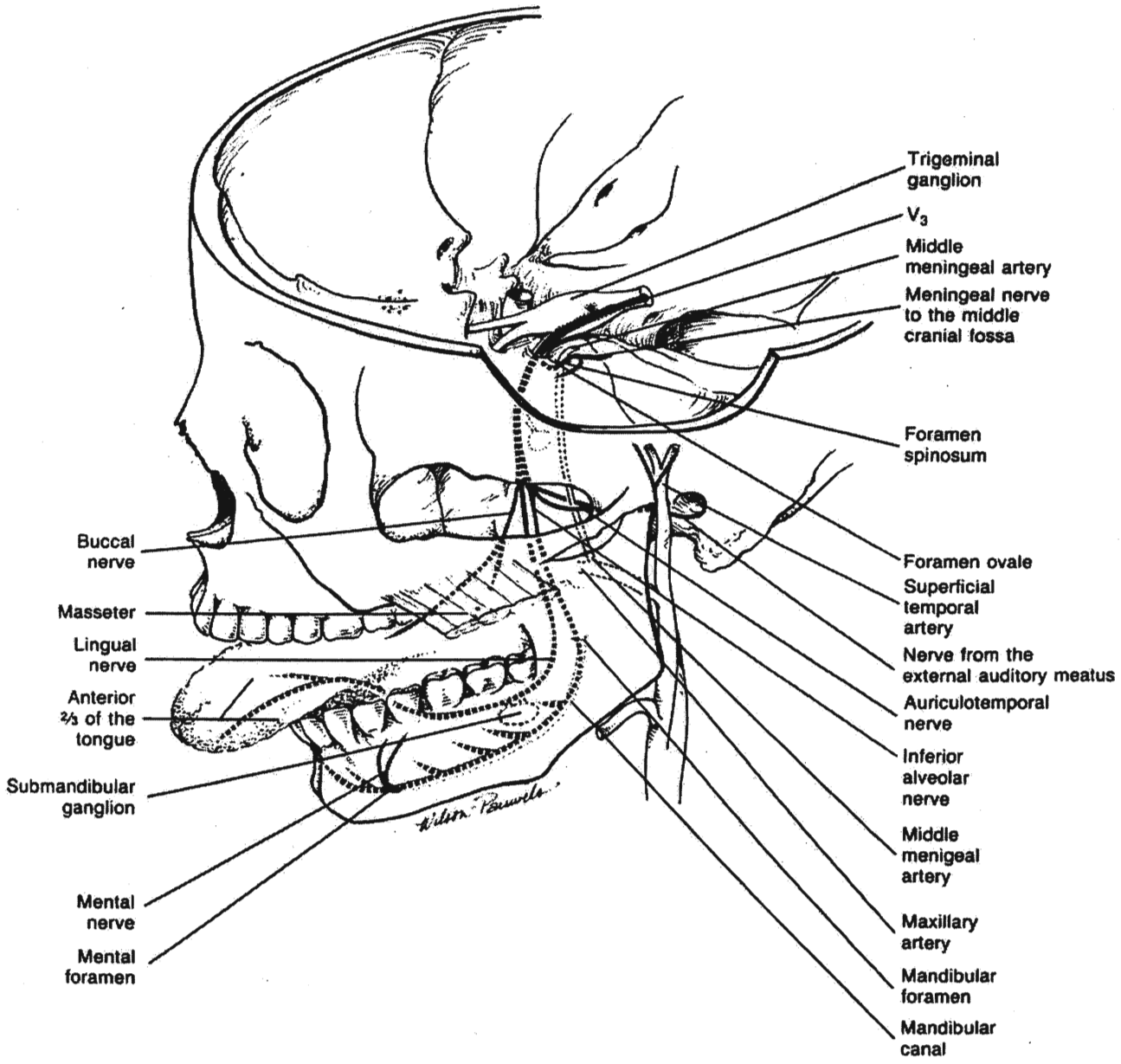
Overview of the Trigeminal Nerve.



Adapted from Wilson-Pauwels, L., Akesson, E.J., & Stewart, P.A. (1988). Cranial nerves: Anatomy and clinical comments. Philadelphia, PA: B.C. Decker Inc. Used with permission.

Figure 2.

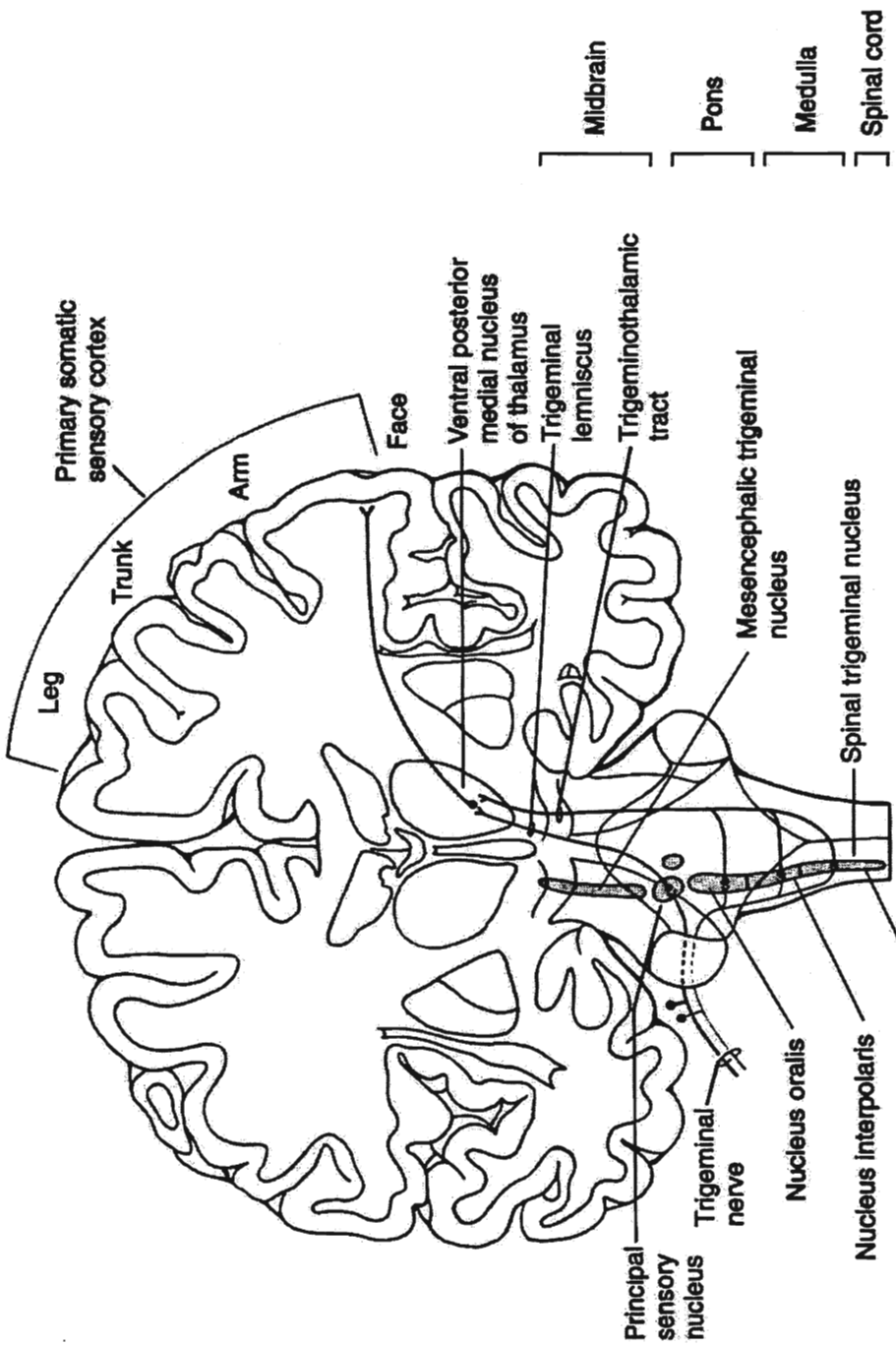
Mandibular Branch of the Trigeminal Nerve.



Adapted from Wilson-Pauwels, L., Akesson, E.J., & Stewart, P.A. (1988) Cranial nerves: Anatomy and clinical comments. Philadelphia, PA: B.C. Decker Inc. Used with permission.

Figure 3.

Anatomical Route of the Trigeminal Nerve to the Somatosensory Cortex.



Adapted from Kandel, E.R., Schwartz, J.H., & Jessel, T.M. (1991). Principles of neural science, 3rd Ed. New York, NY: The McGraw-Hill Companies. Used with permission.

Figure 4.

Diagrammatic Representation of Trigeminal Stimulation and Recording Apparatus.

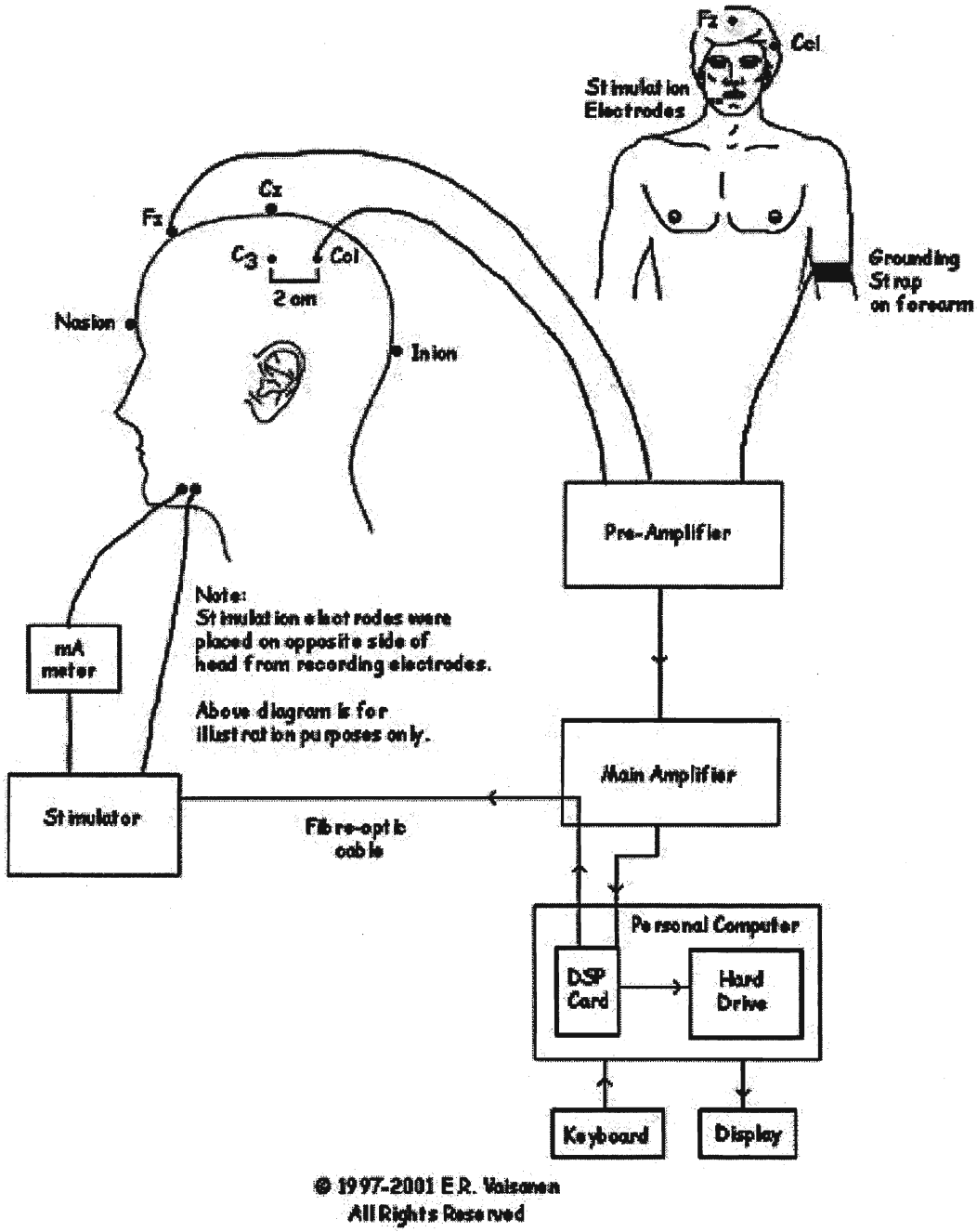


Figure 5.

Amplifier-generated artifact due to amplifier overload.

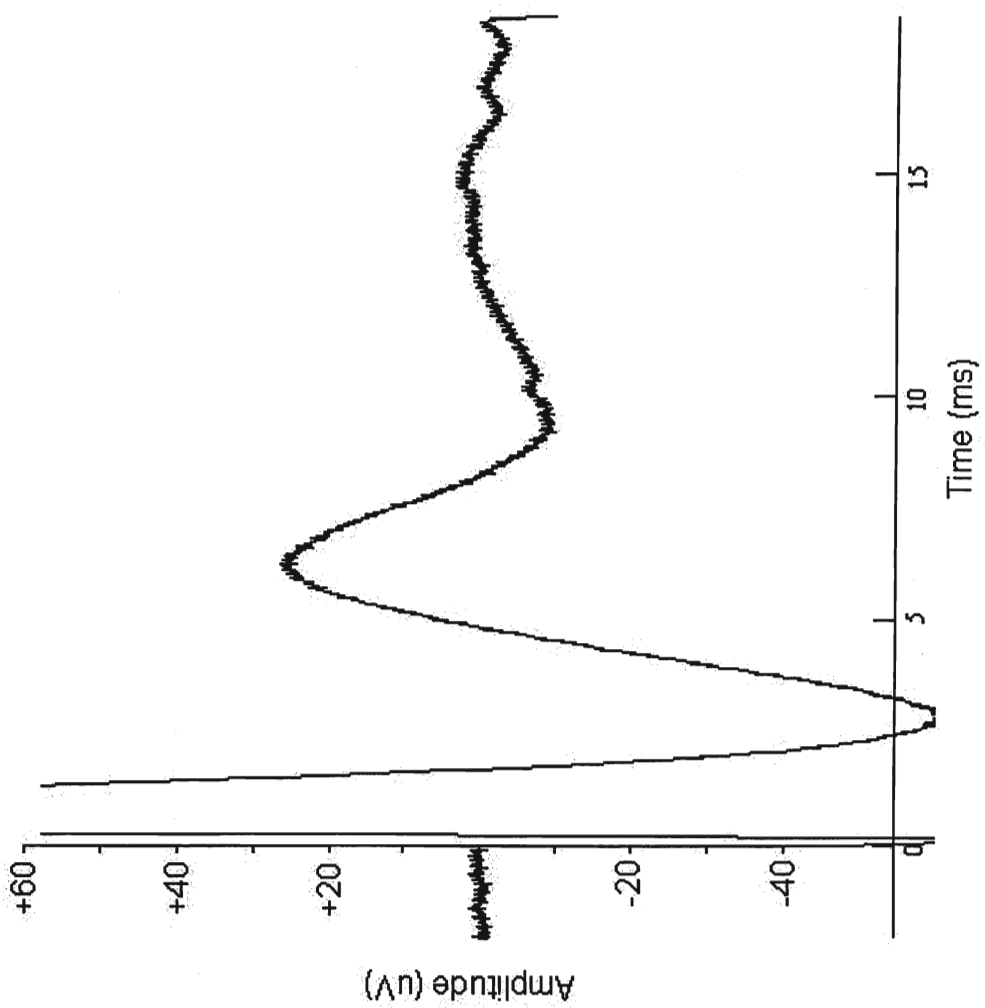


Figure 6.

Reduced artifact through alternating polarity manual trial.

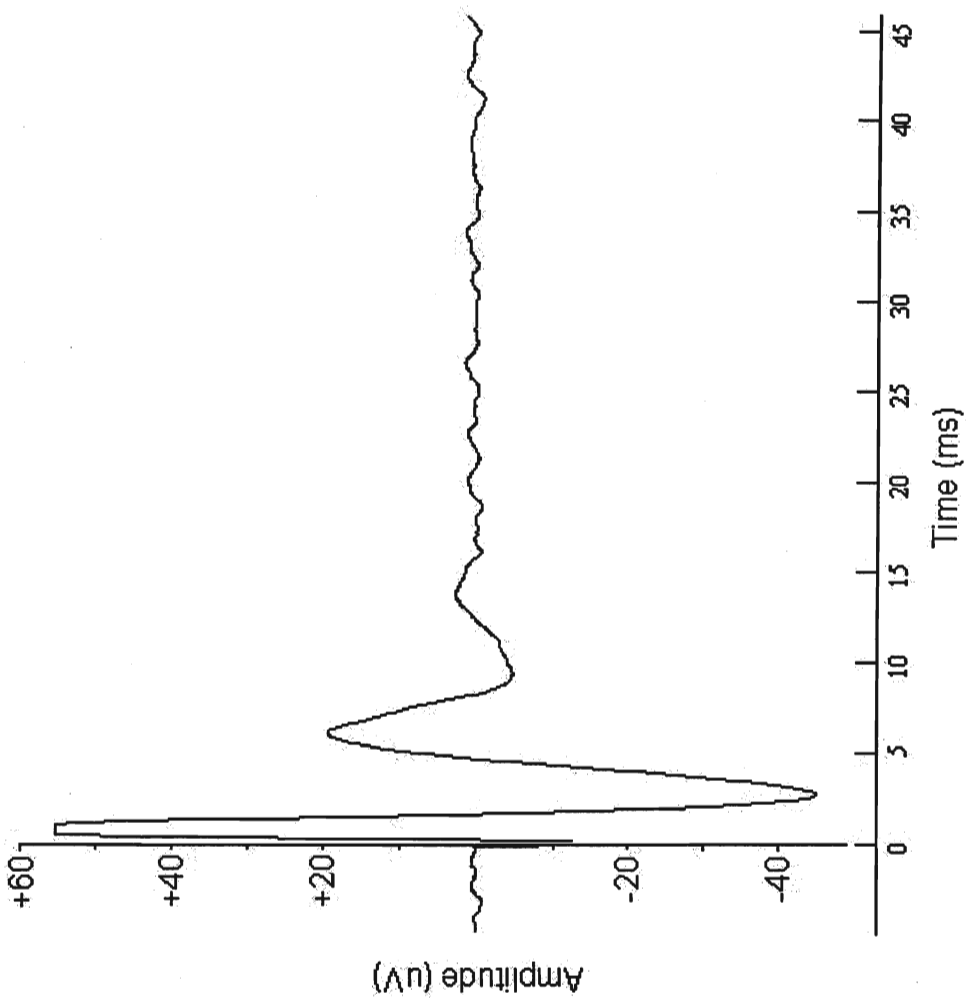


Figure 7.

Reduced artifact through alternating stimulus polarity.

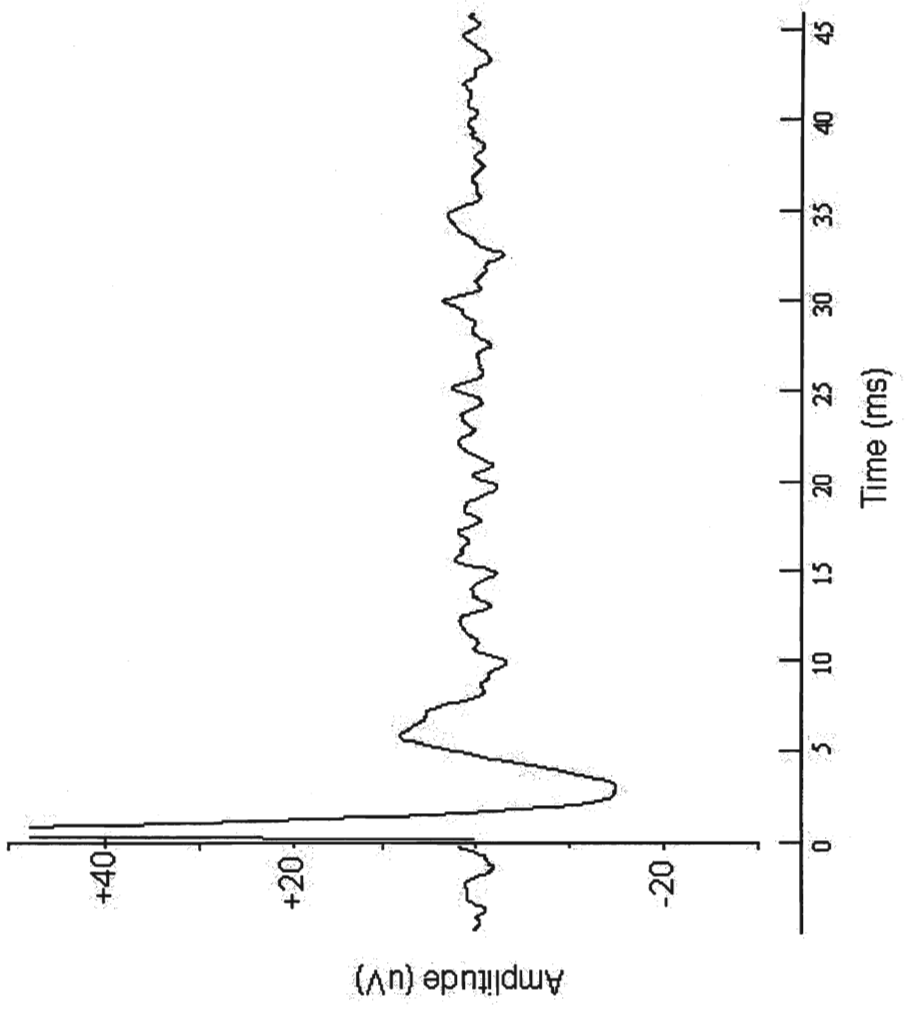


Figure 8.

Normal 10 mA current pulse on chicken thigh.

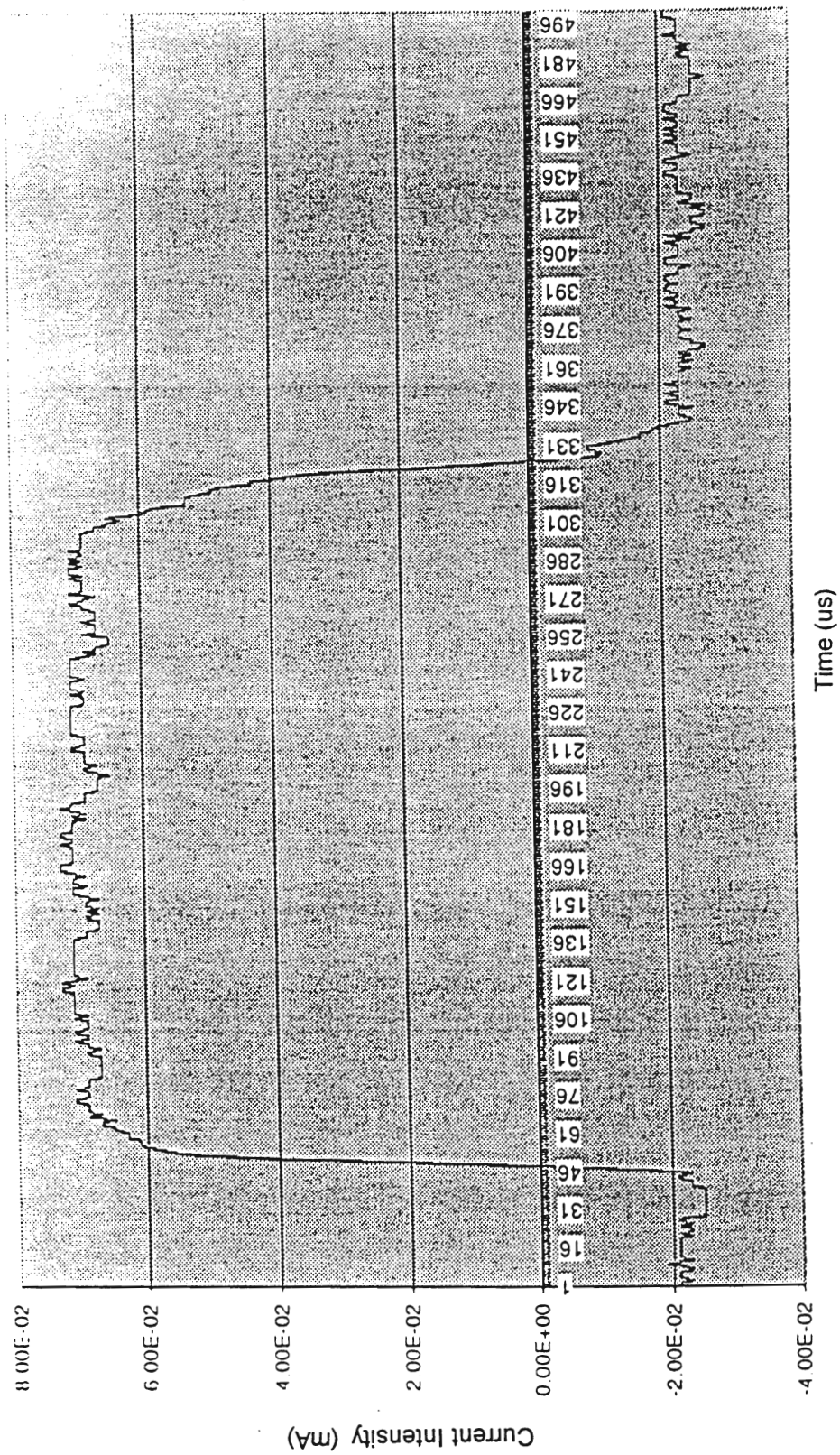


Figure 9.

Normal 10 mA current pulse on human wrist.

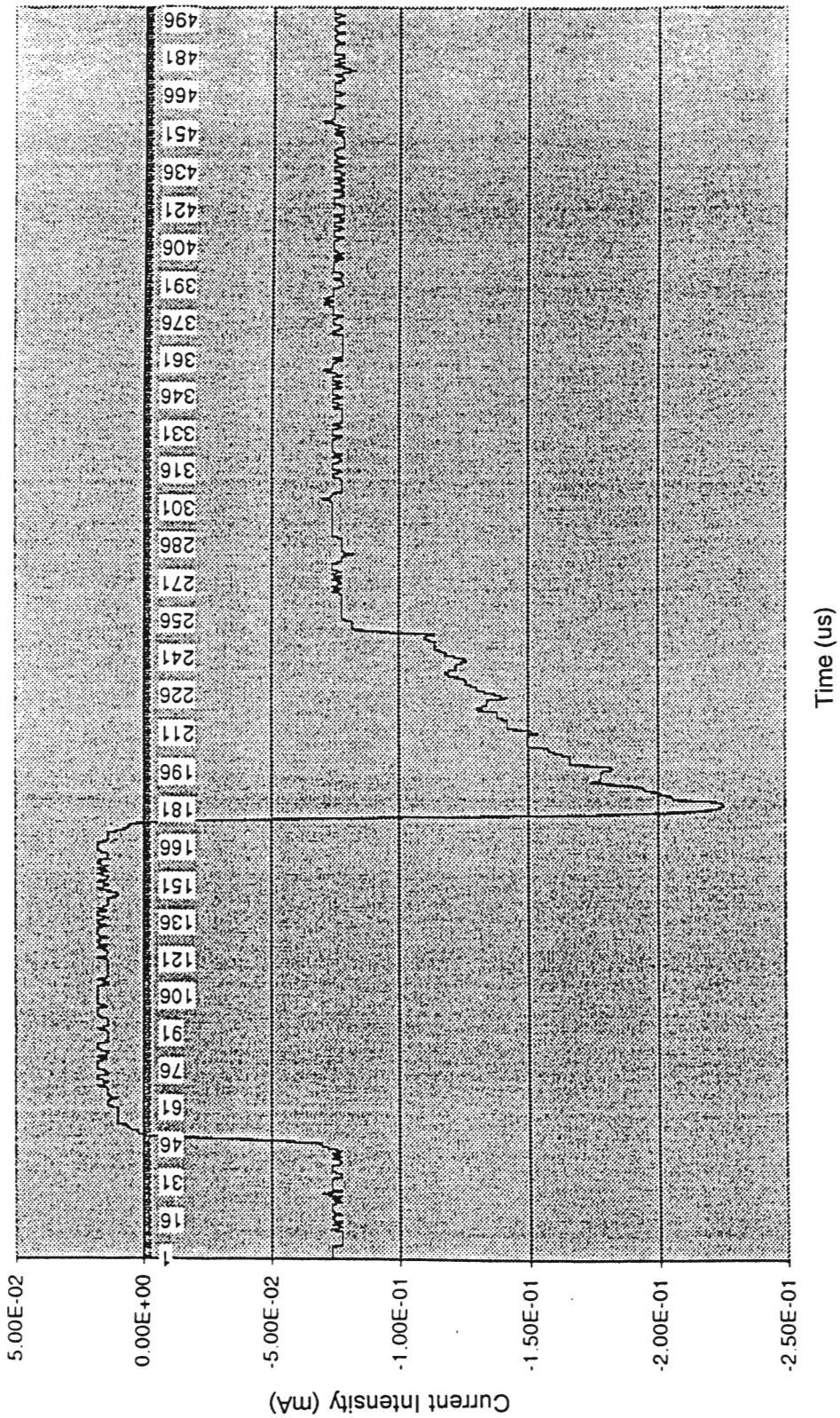


Figure 10.

Breakdown of 20 mA current pulse on human wrist.

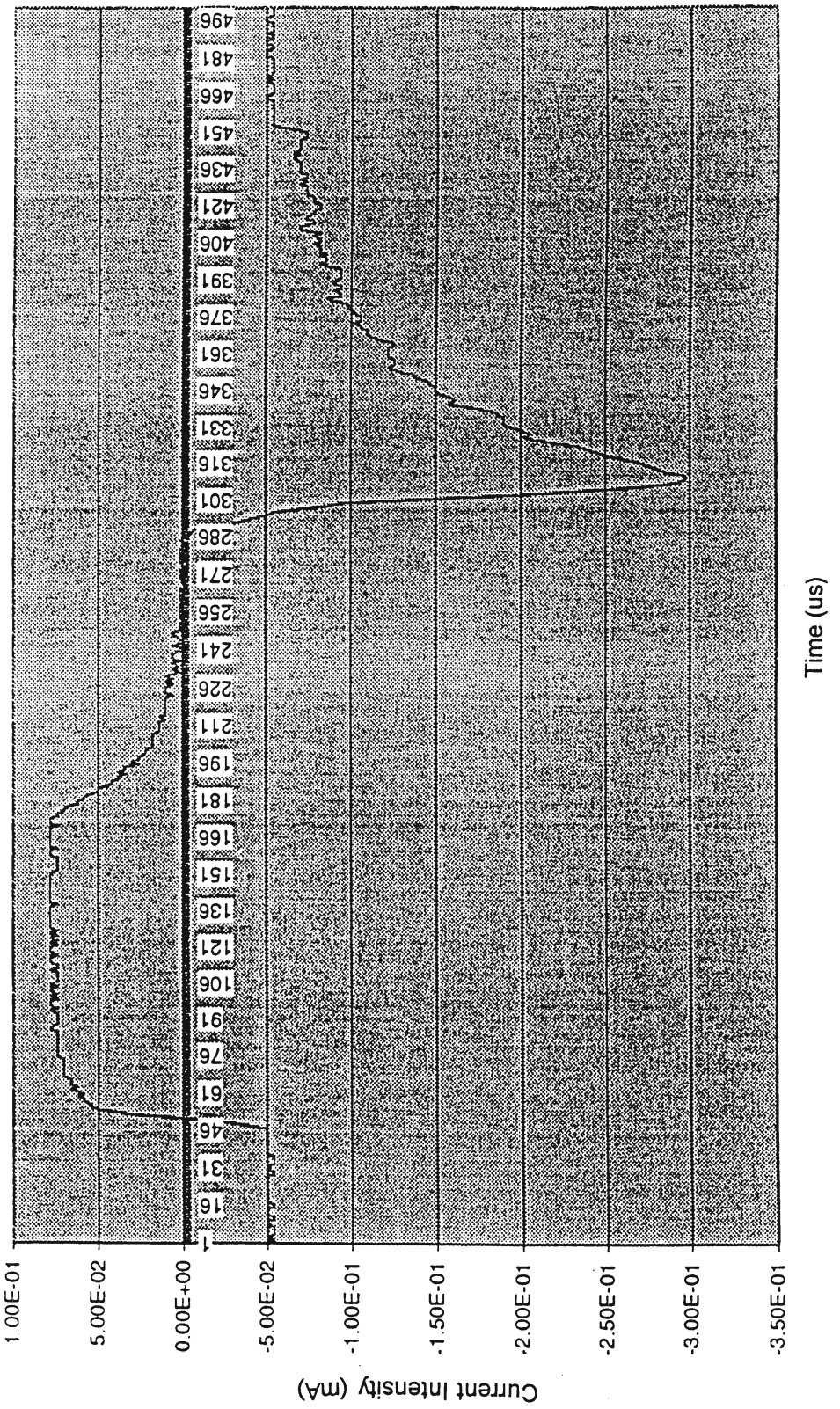


Figure 11.

Single frame representation of EMG movement artifact.

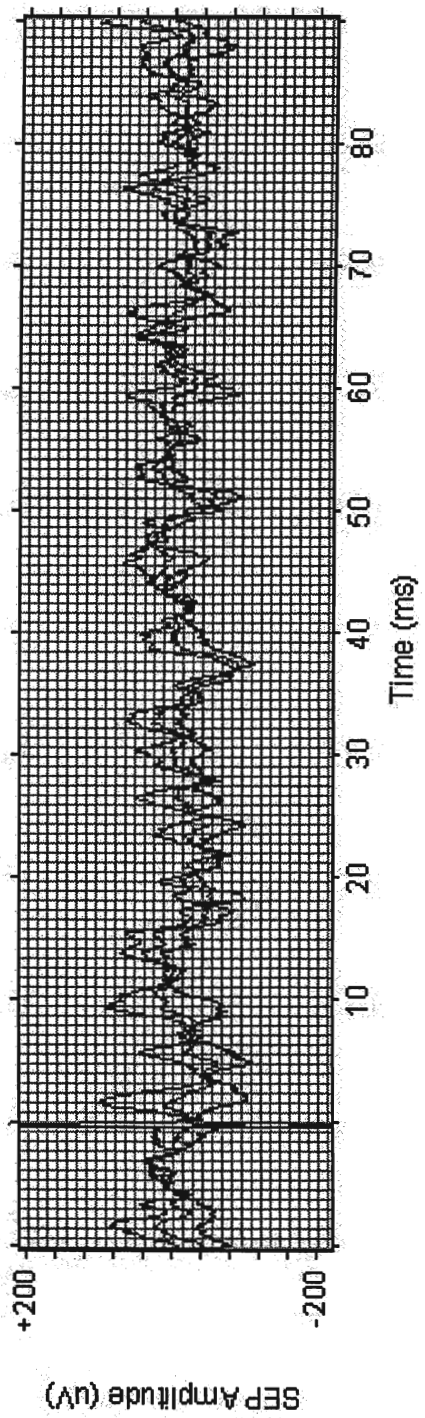


Figure 12.

Robust TSEP waveform in top frame and arithmetically-diluted average in bottom frame.

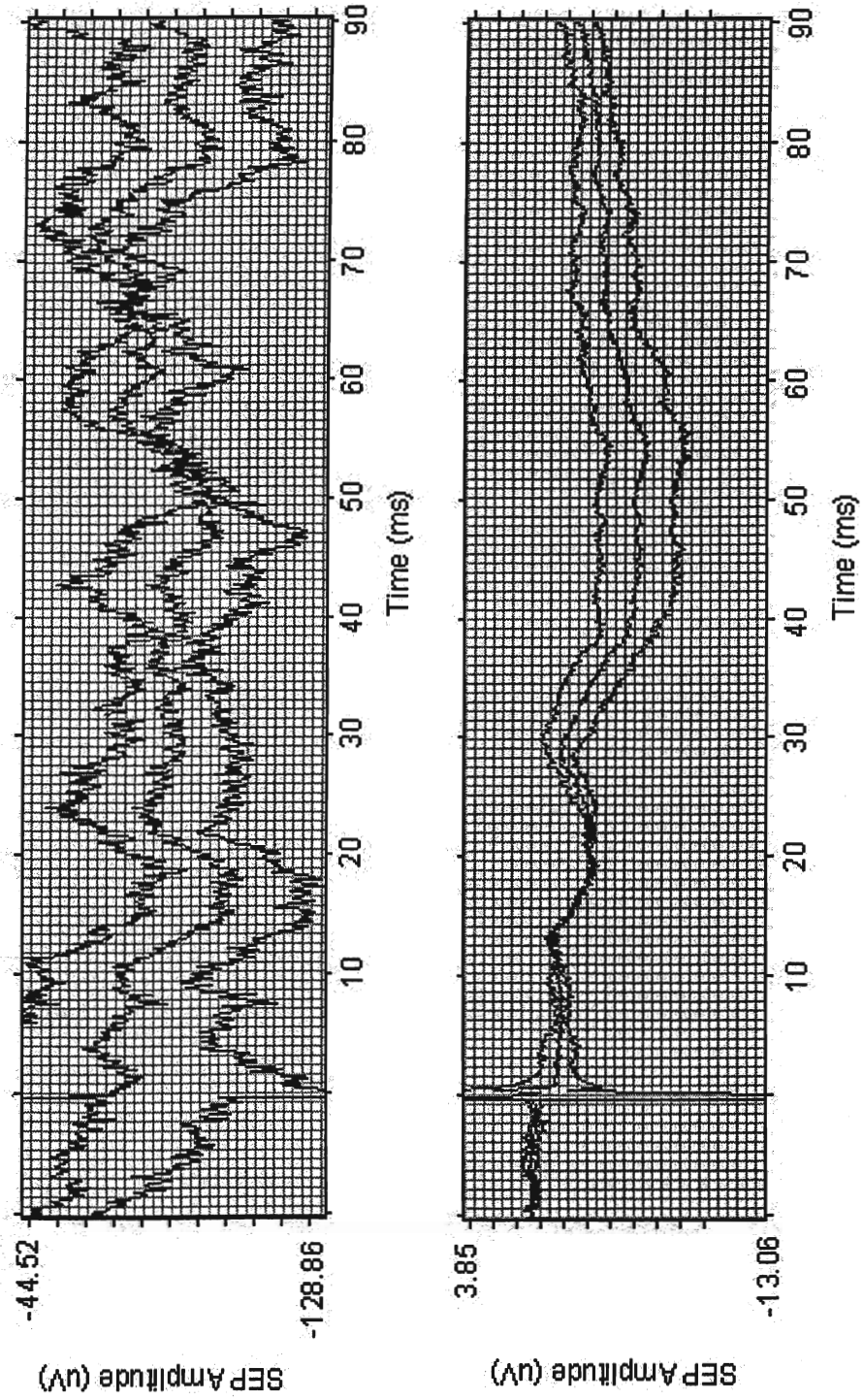


Figure 13.

Absence of waveform due to low amplifier gain.

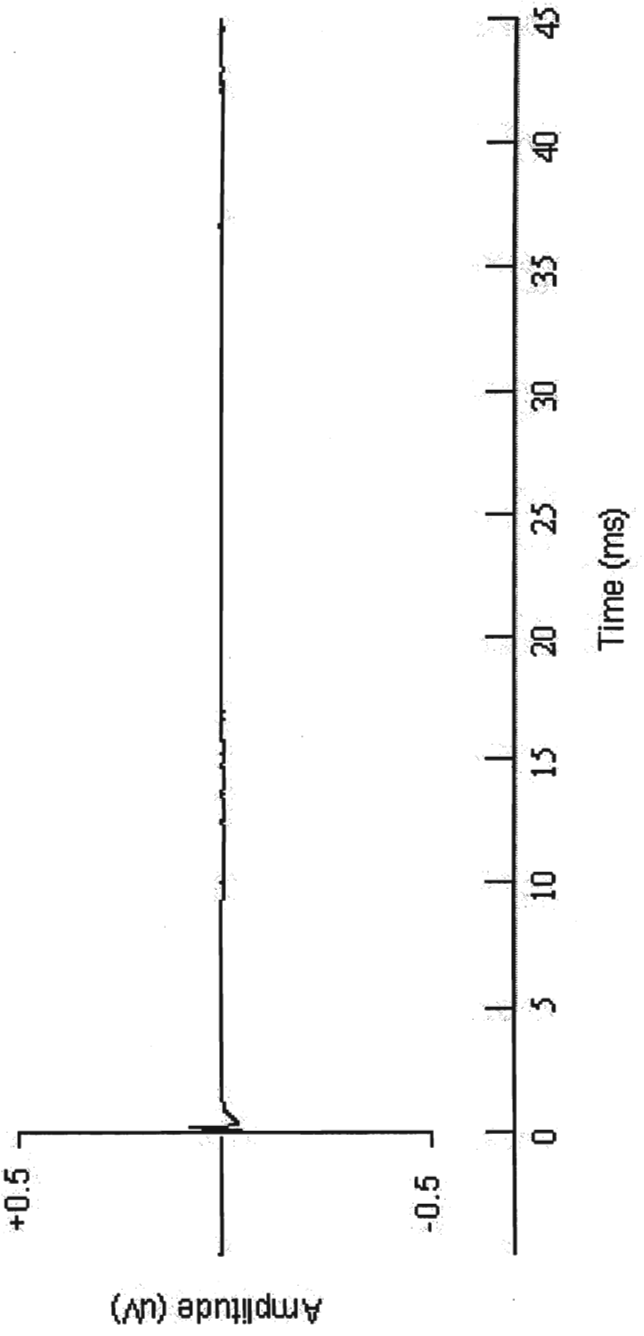


Figure 14.

Stimulus artifact with high frequency contamination overlay.

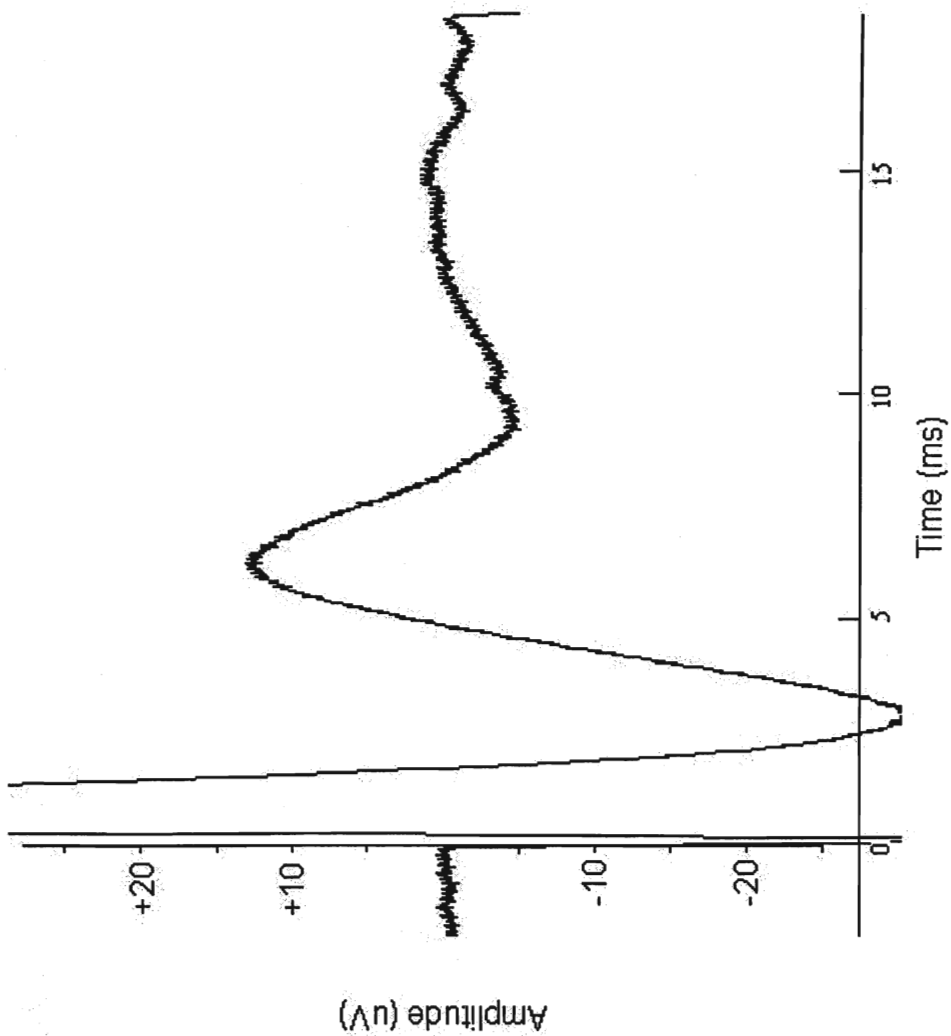


Figure 15.

Massive stimulus artifact recorded over a 50 ms epoch.

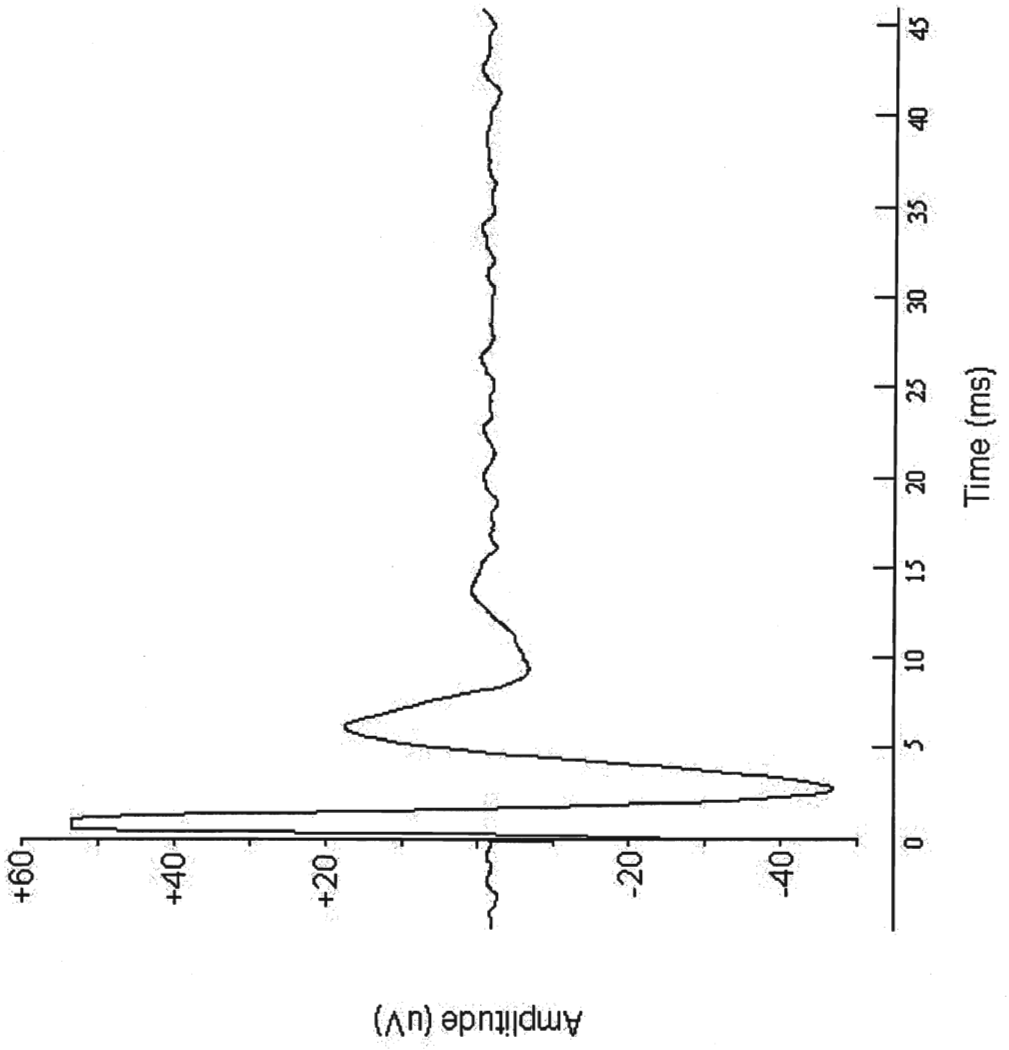


Figure 16.

Reduced stimulus artifact after amplifier gain correction.

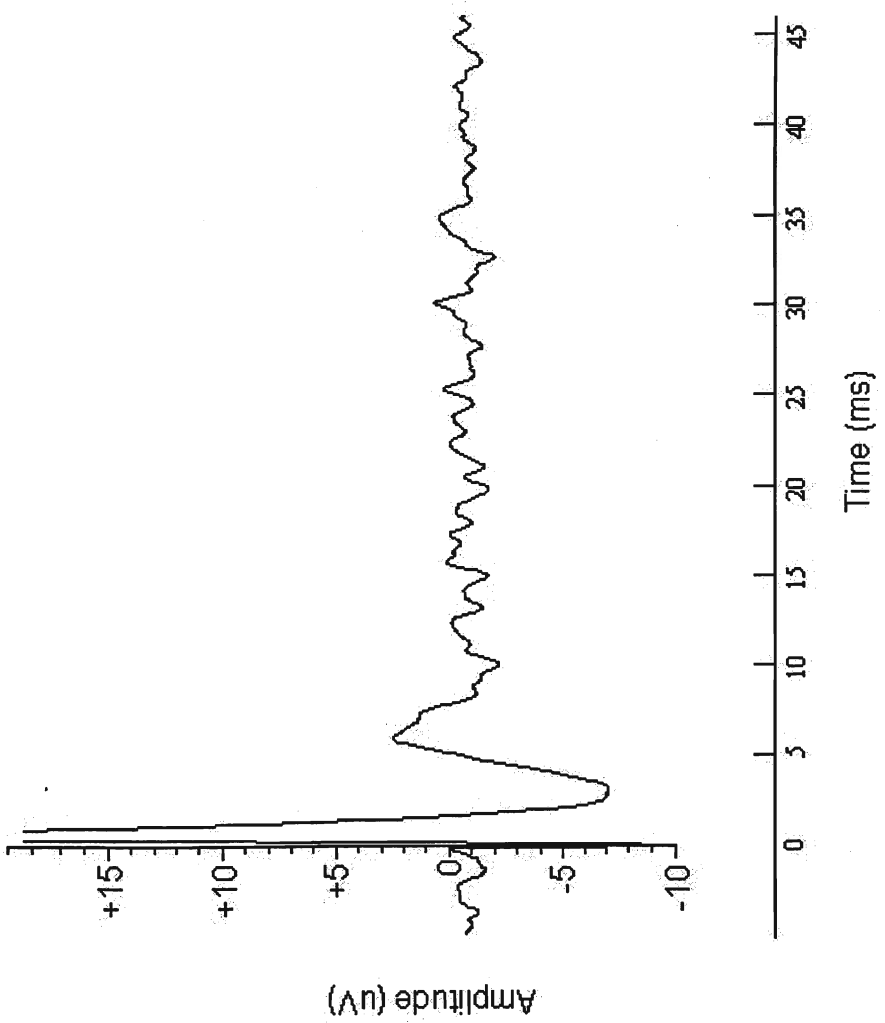


Figure 17.

Waveform illustrating amplifier ringing and high frequency contamination.

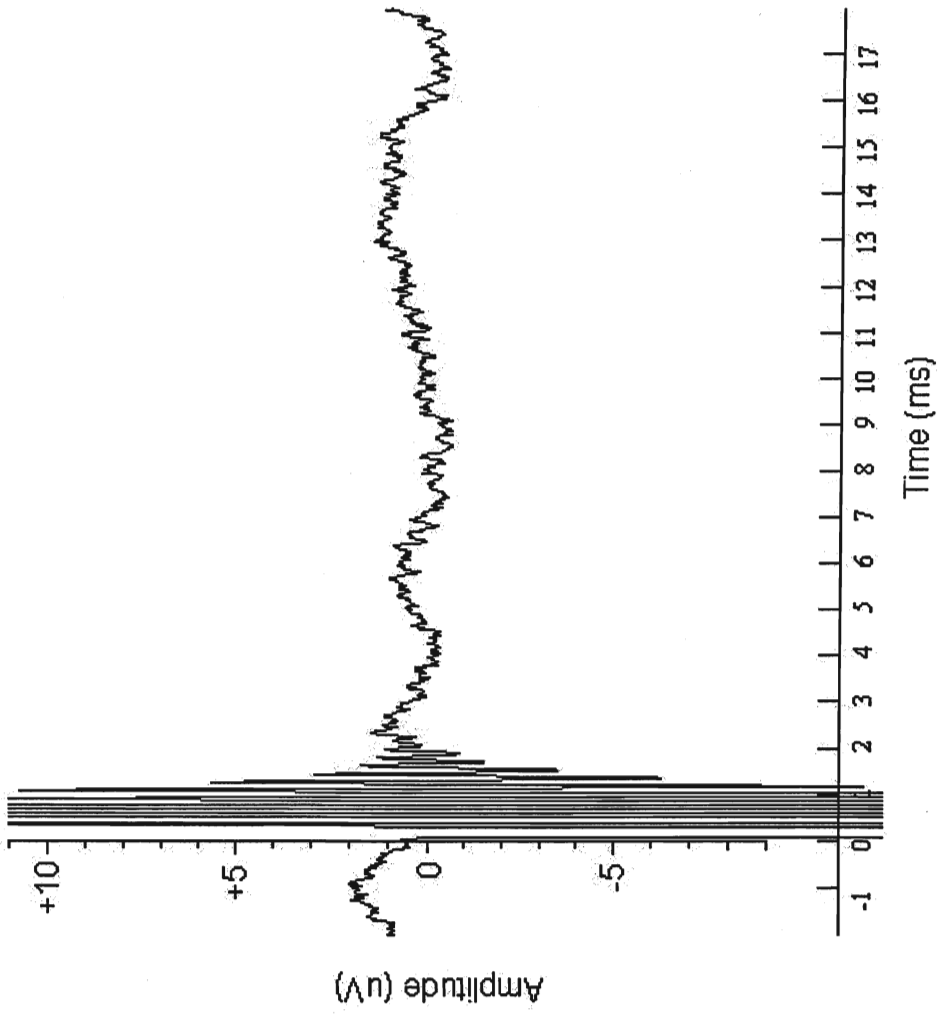


Figure 18.

AC-coupled filter generated slow-wave decay artifact.

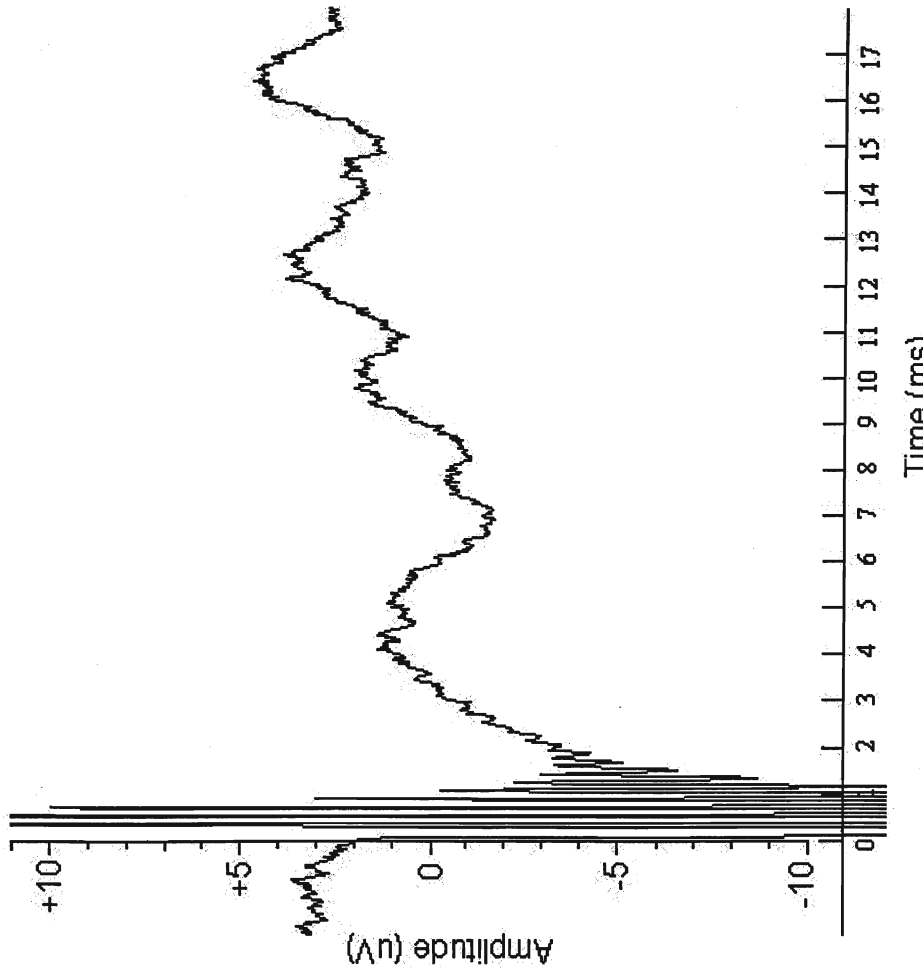


Figure 19.

Heavy RFI noise contamination following bandpass filter removal.

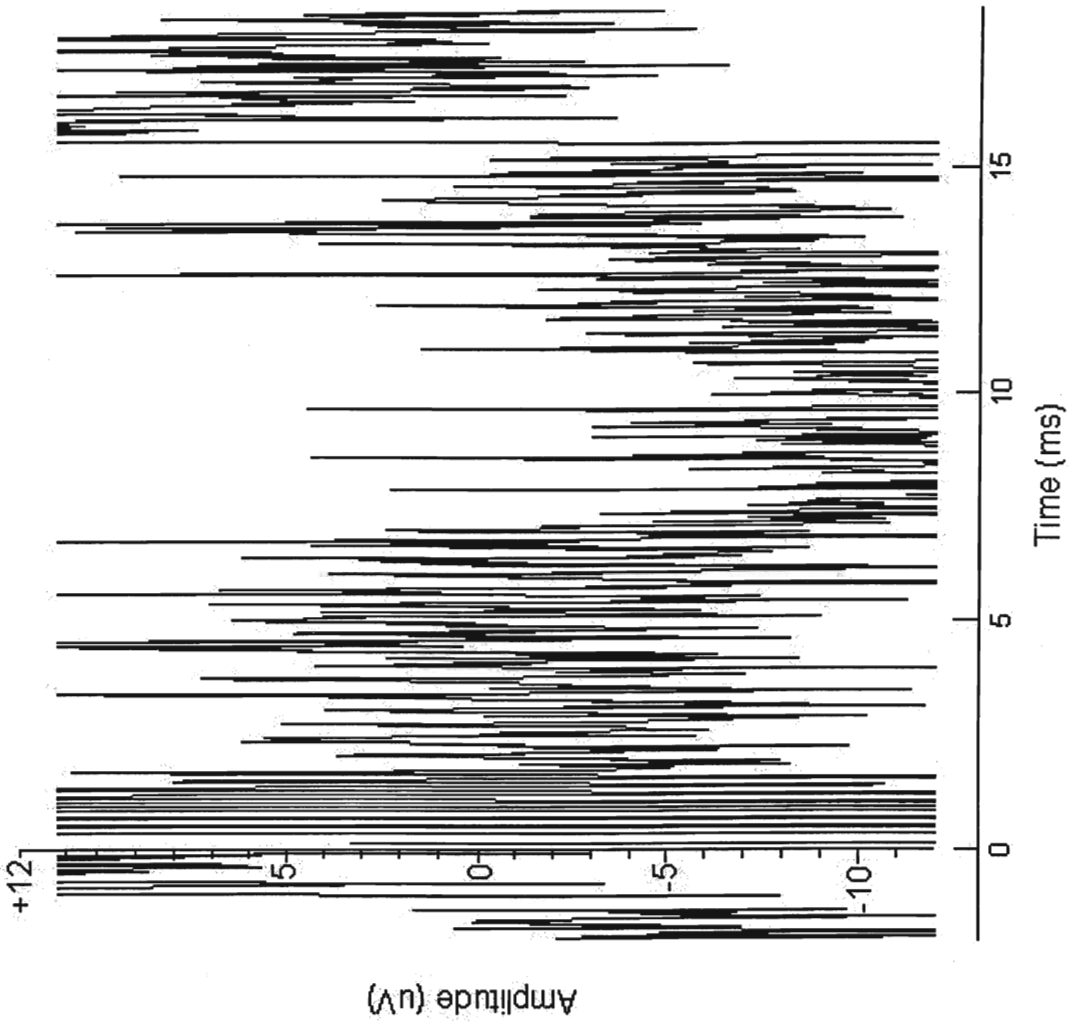


Figure 20.

Emerging SEP waveform with lower cortical electrode impedances.

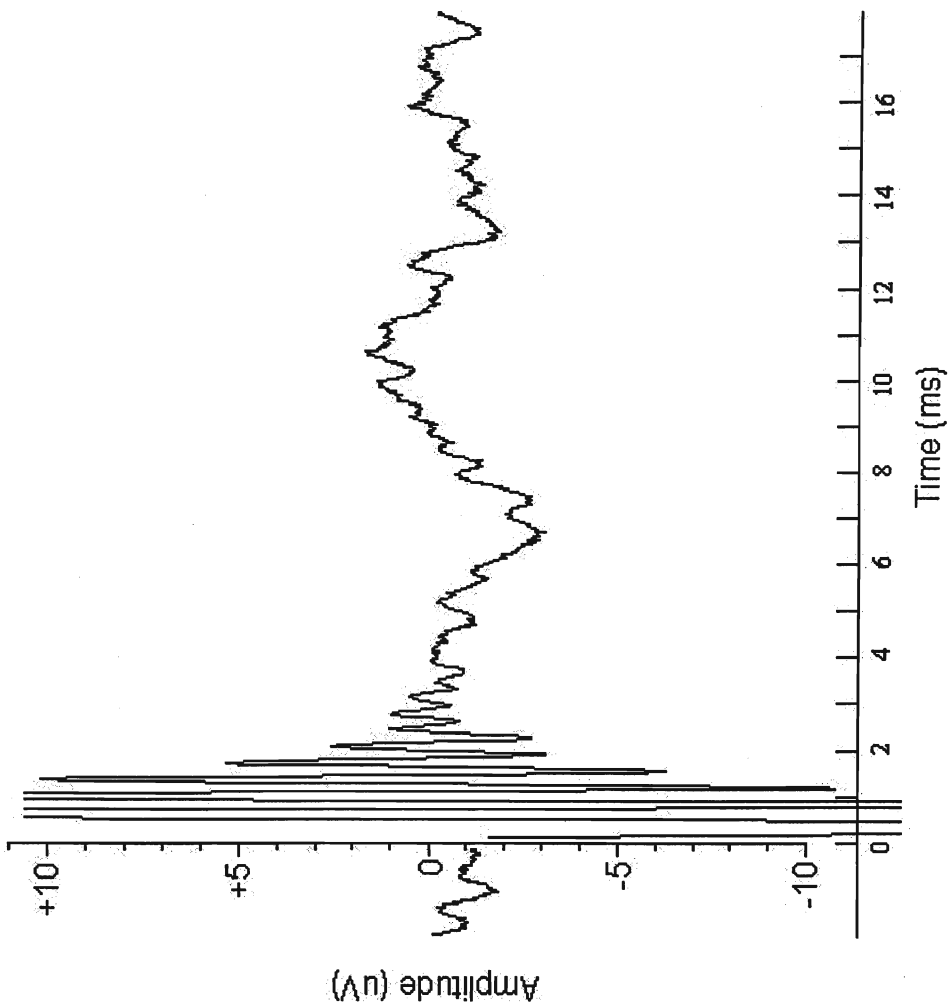


Figure 21.

Unreproducible waveform - trial 1.

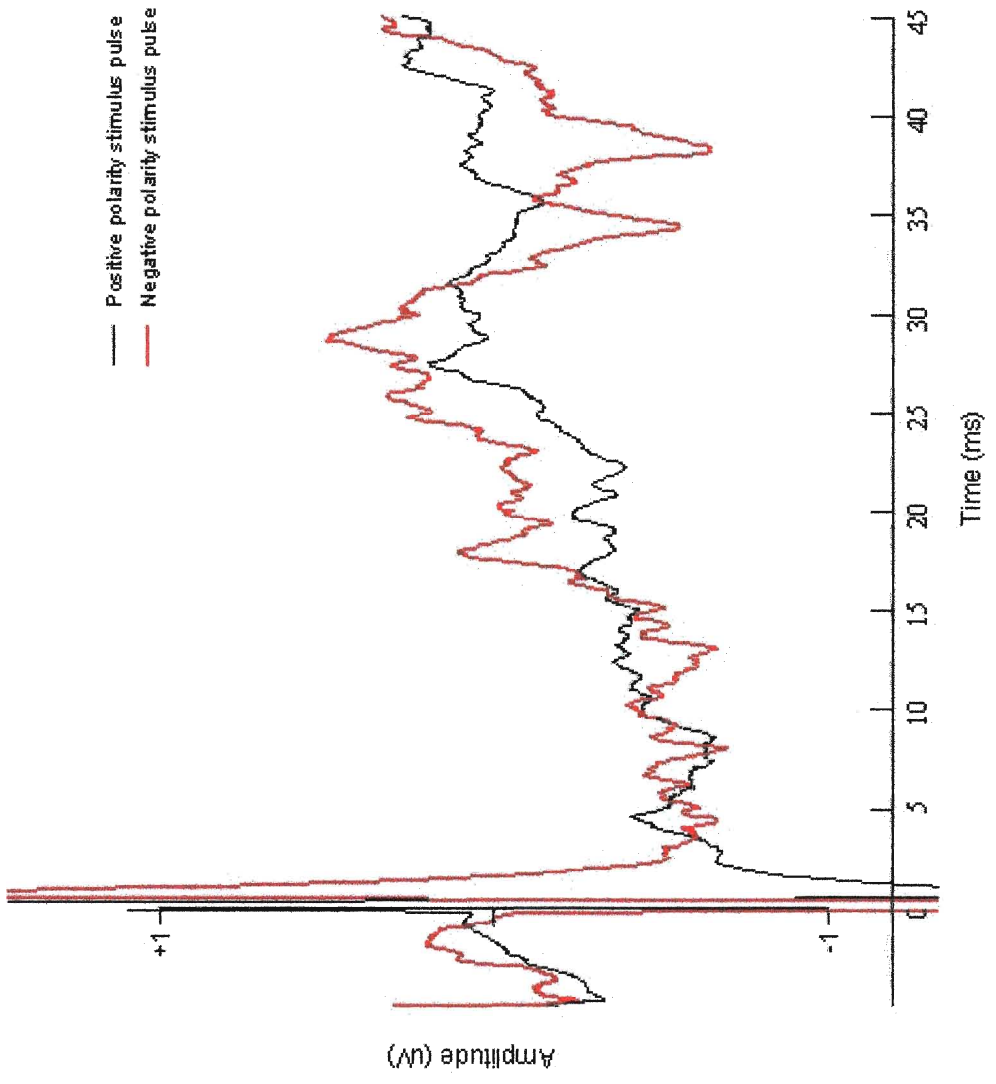


Figure 22.

Unreproducible waveform - trial 2.

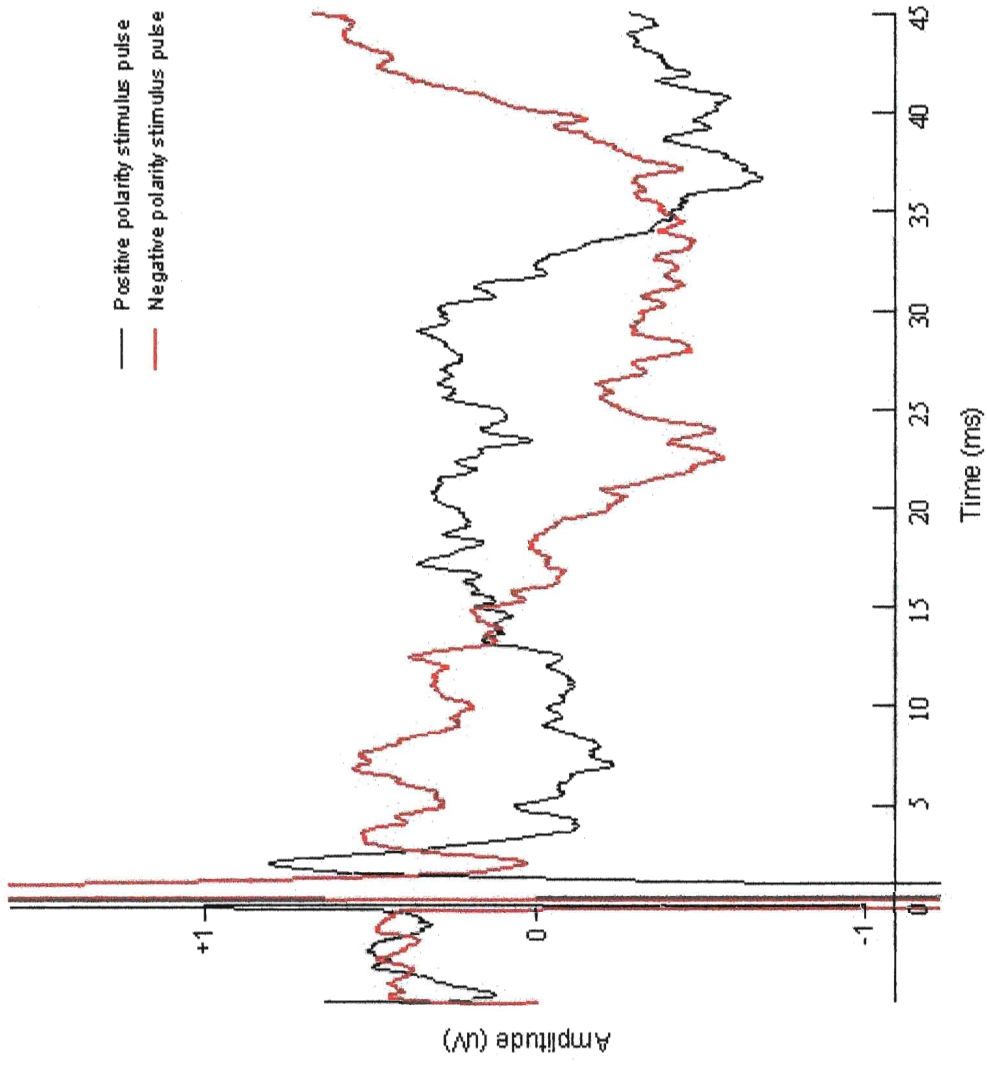


Figure 23.

Waveform illustrative of data corruption due to data drop out.

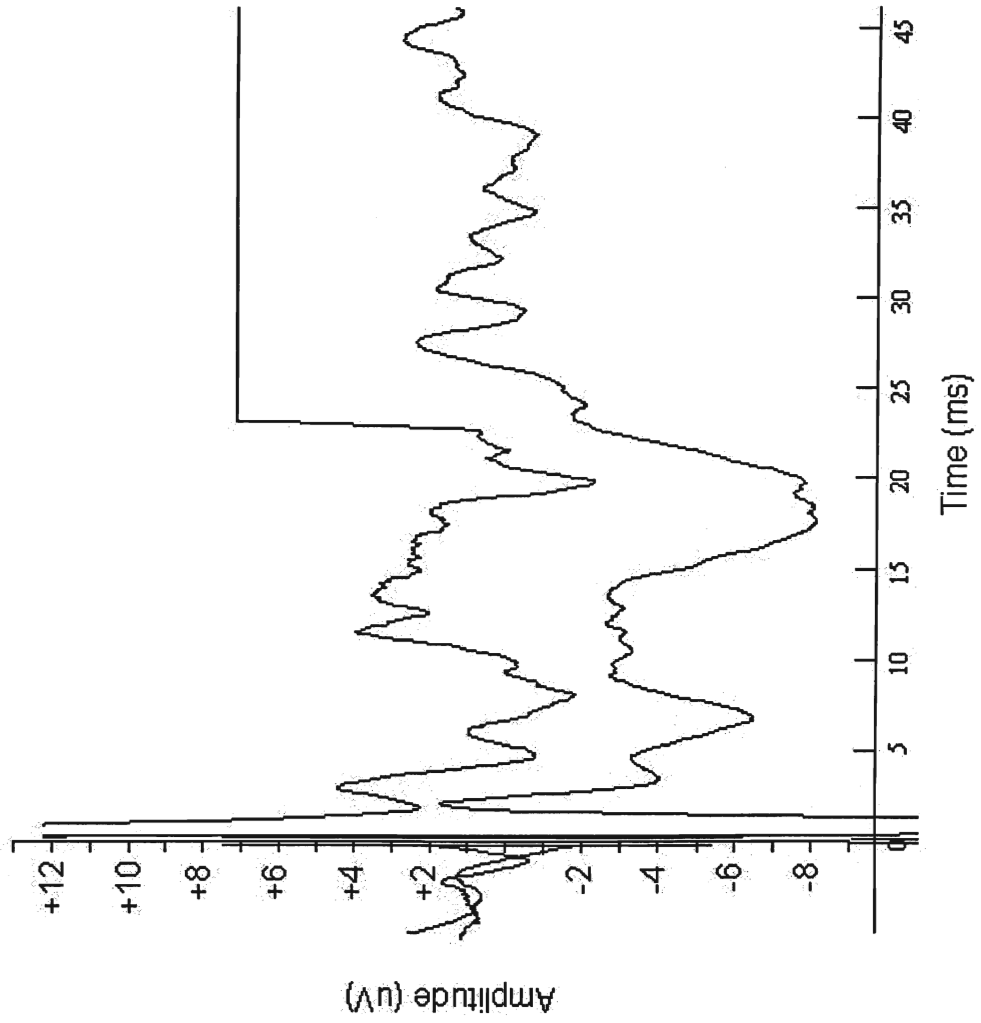


Figure 24.

Emerging TSEP waveforms from separate stimulus pulse recording.

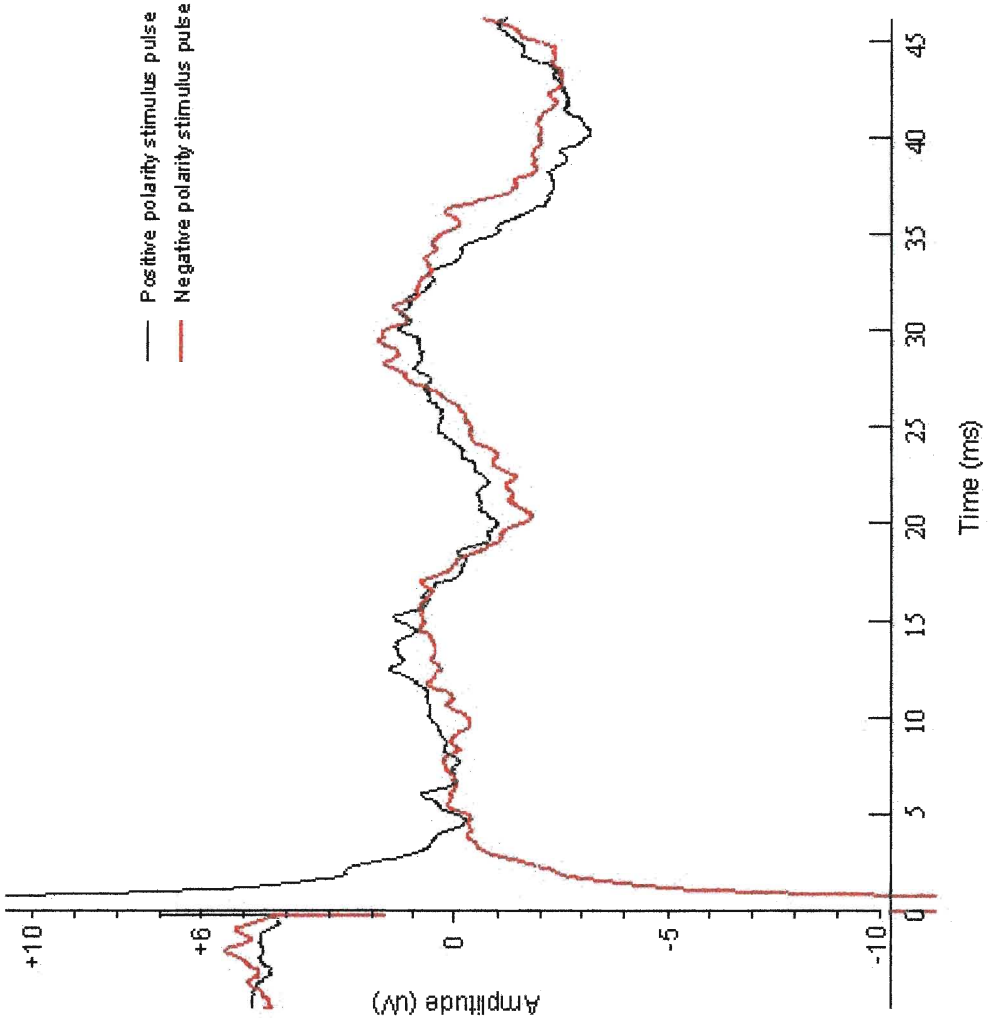


Figure 25.

Mathematical average of separate pulse waveforms in Fig. 24.

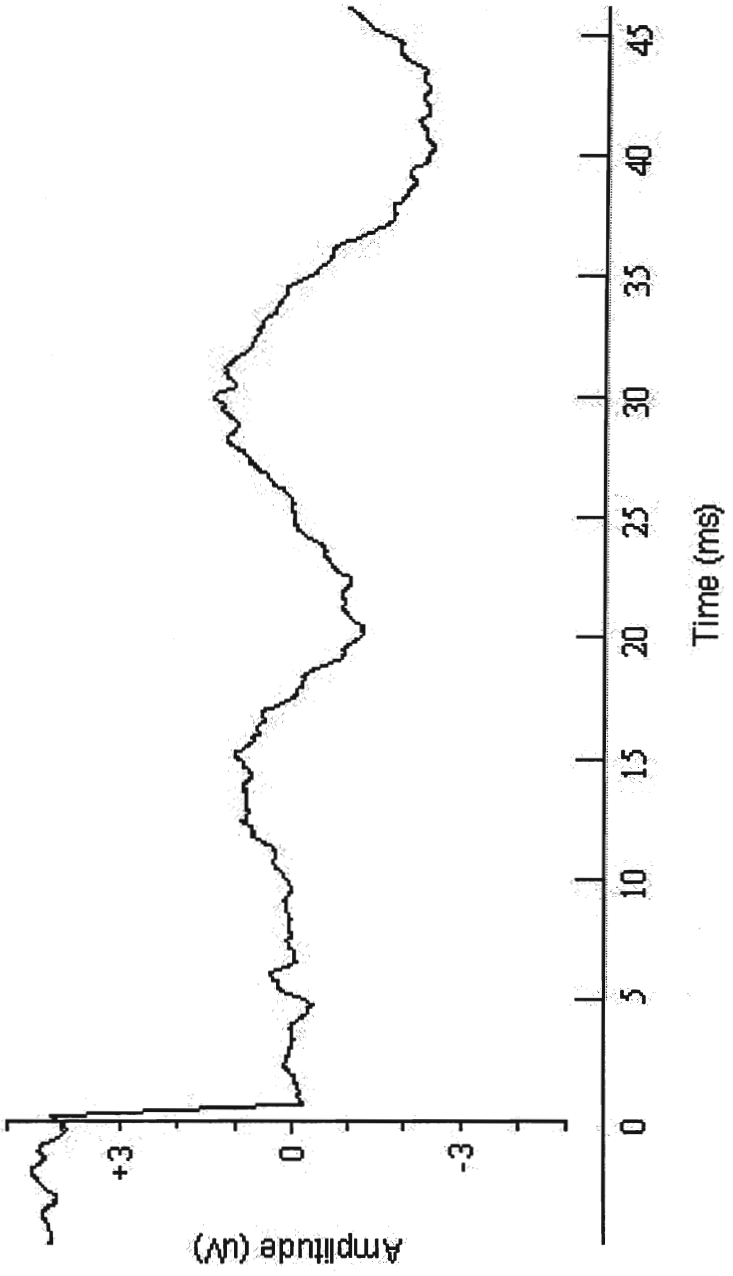


Figure 26.

TSEP waveform from Cc cortical recording site.

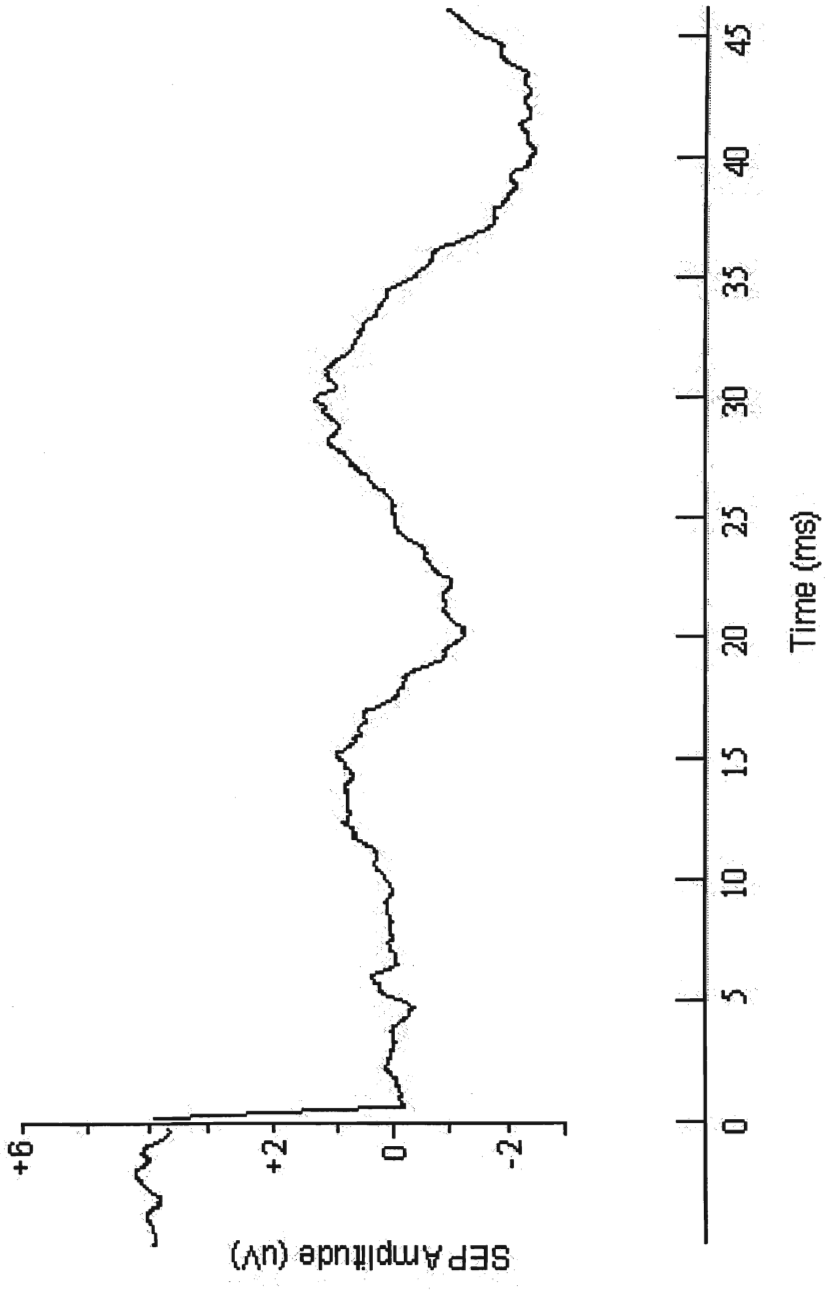


Figure 27.

High frequency contamination from poor cortical recording electrode impedance.

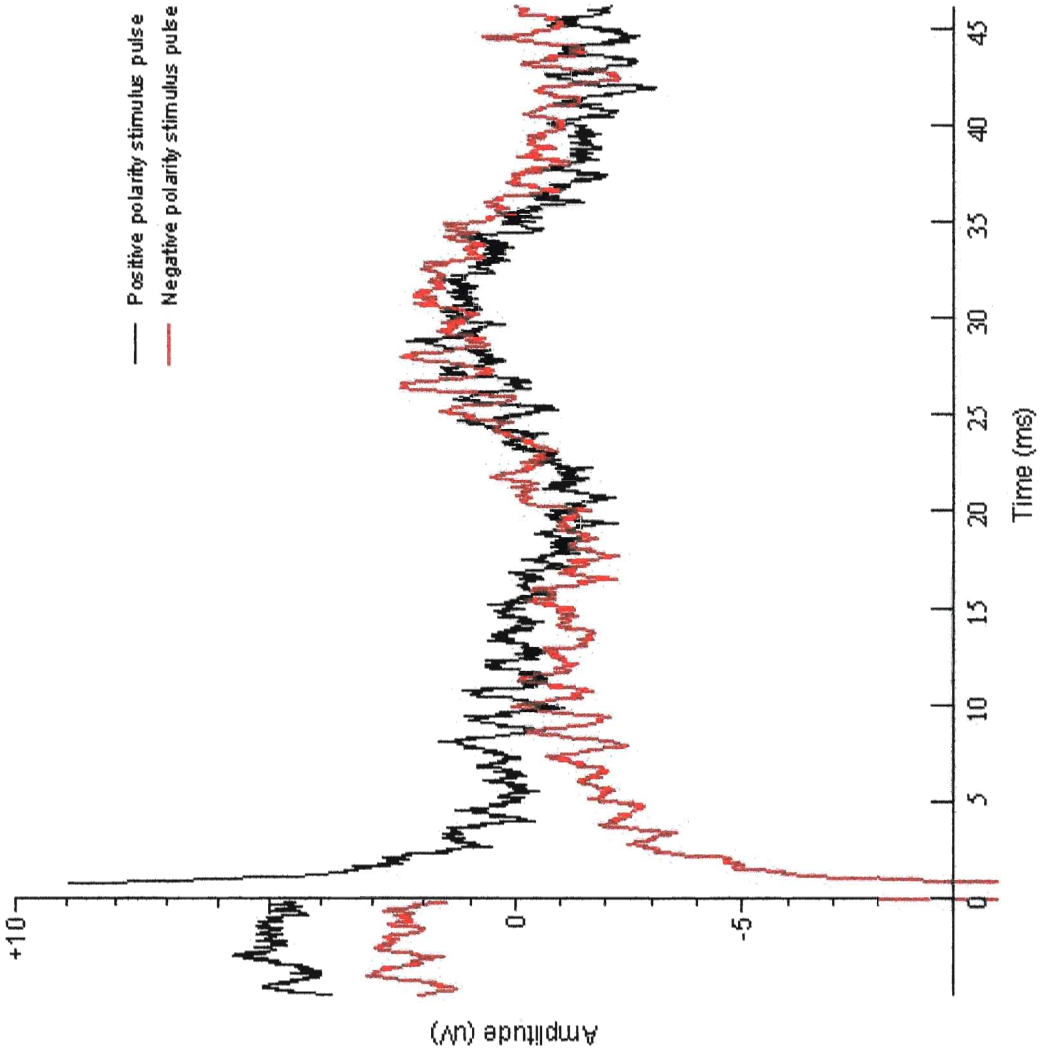


Figure 28.

Remaining noise contamination in Fig. 27 after application of nine-point rolling average filter.

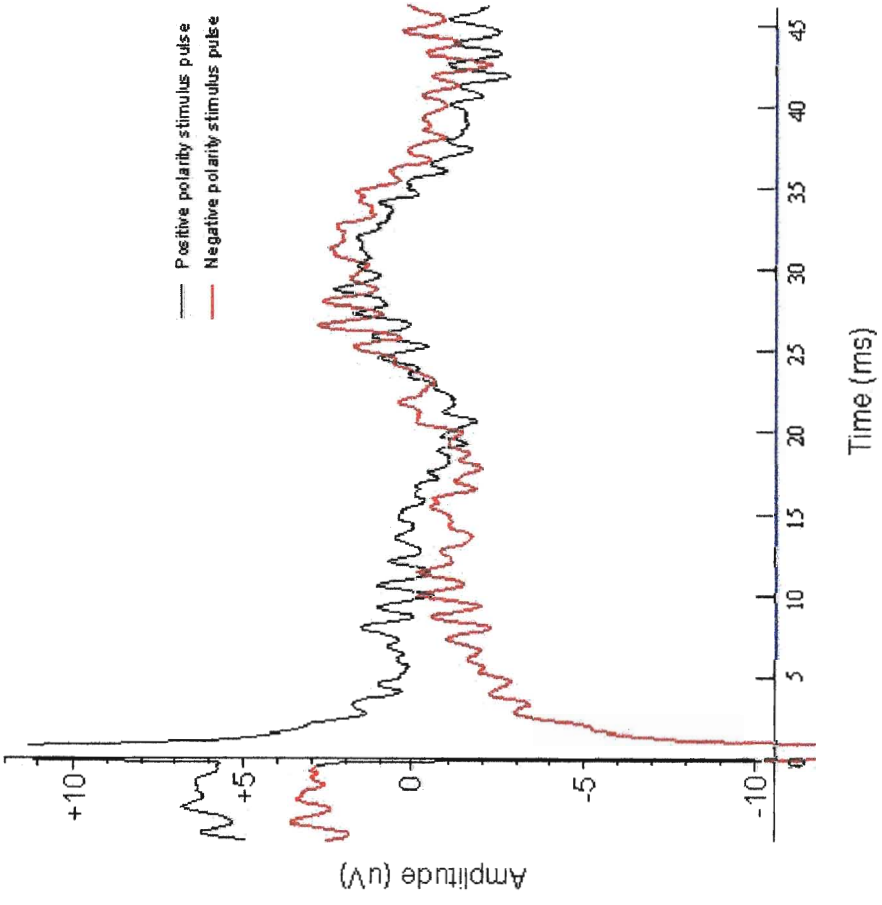


Figure 29.

Separate pulse trials from erroneously landmarked cortical recording sites.

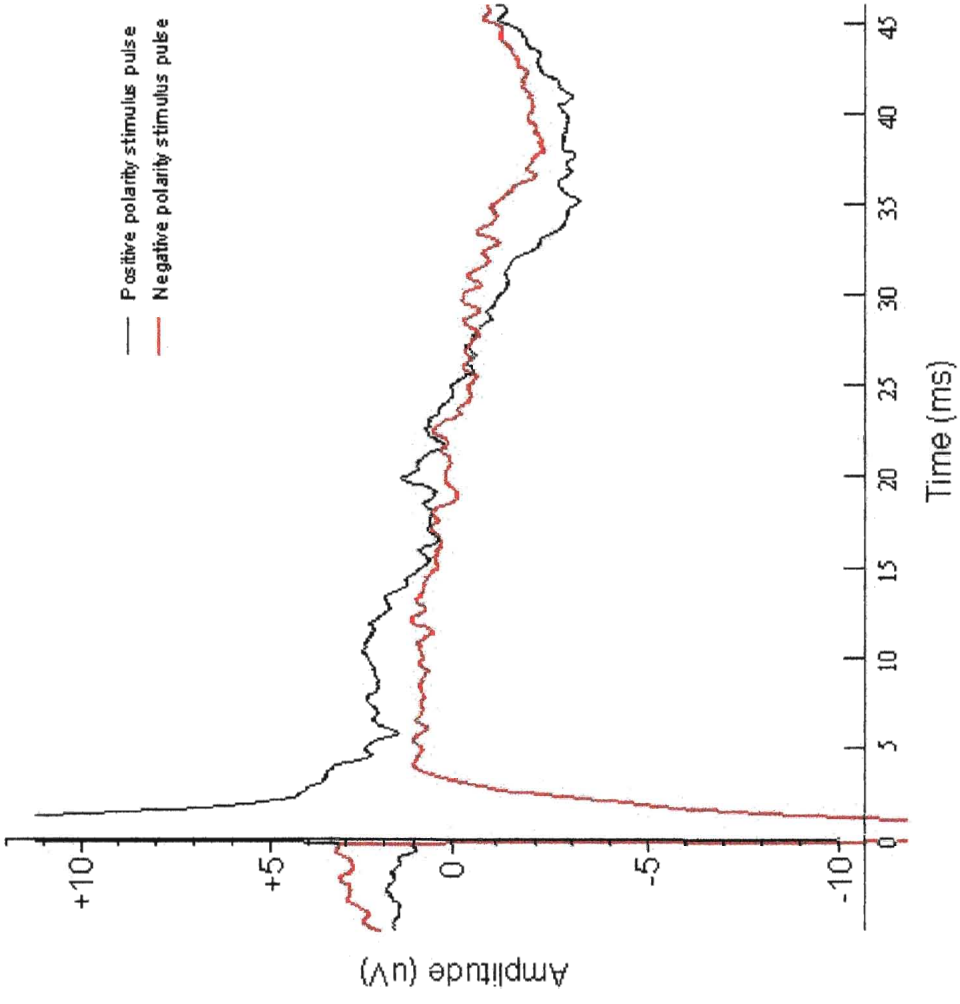


Figure 30.

Averaged waveform from erroneously landmarked cortical recording sites in Fig. 29.

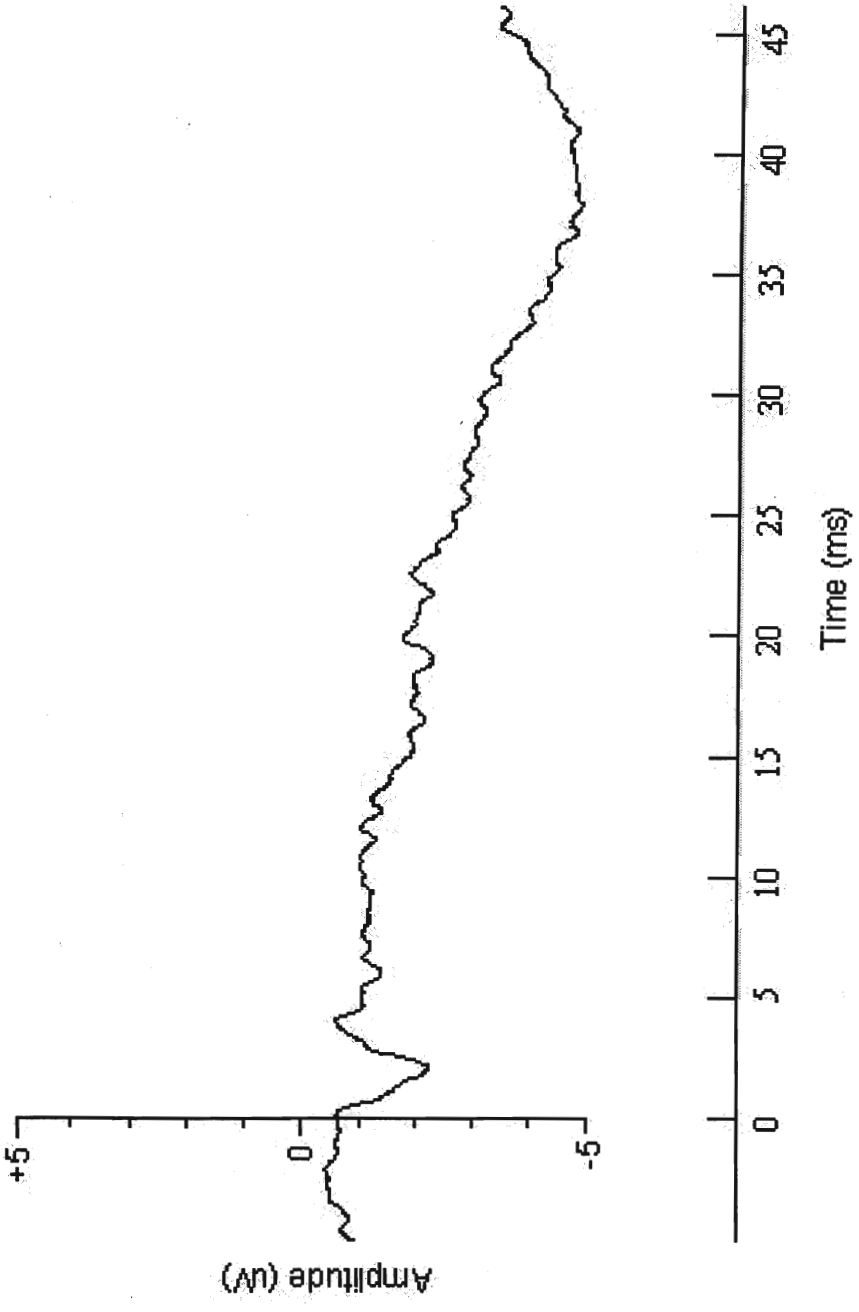


Figure 31.

Single trial waveform with evident 60 Hz contamination.

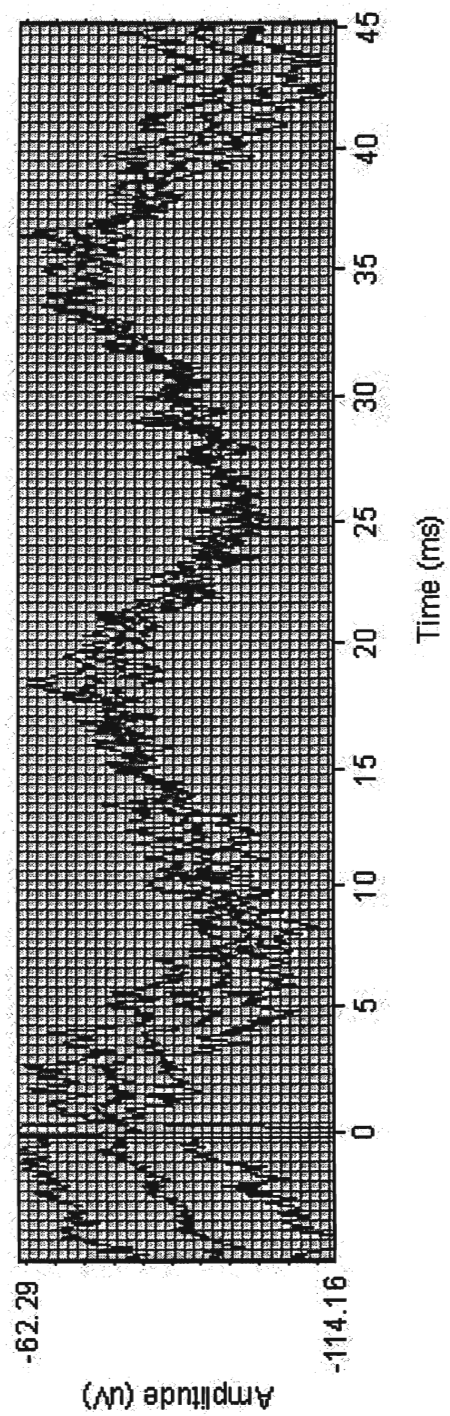


Figure 32.

Waveform contaminated with 60 Hz noise due to poor ground electrode impedance.

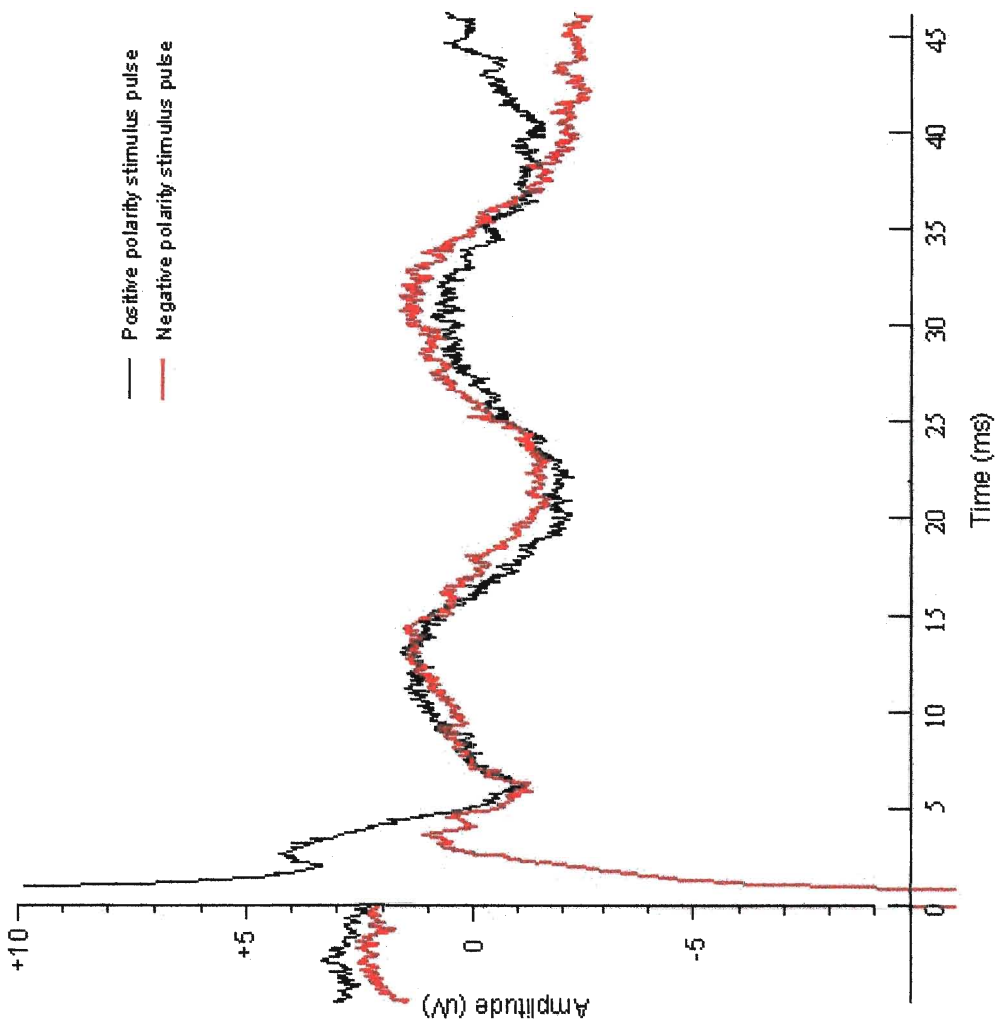


Figure 33.

Waveform arising from initial lip stimulation trial.

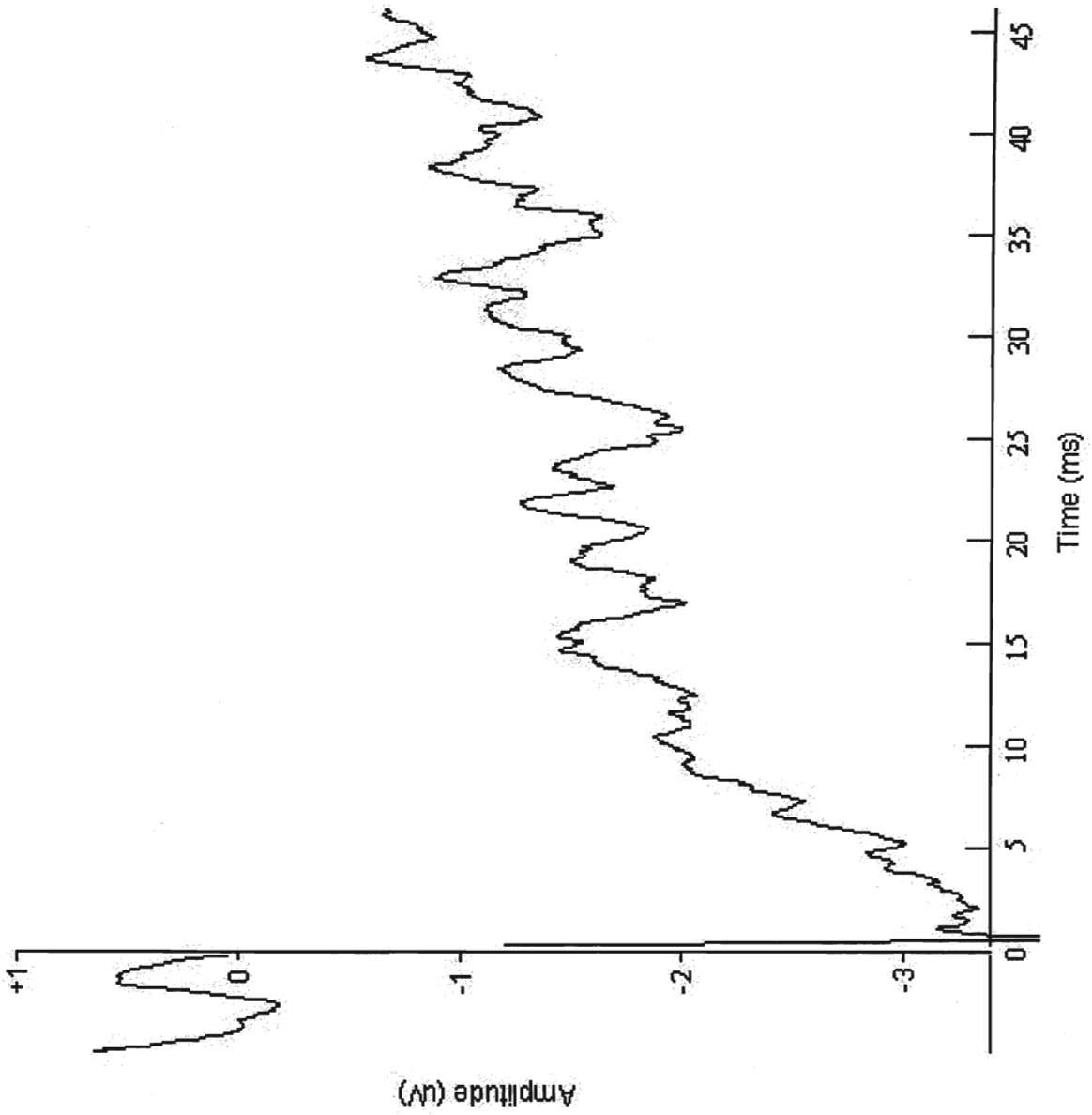


Figure 34.

Waveform arising from erroneous lip placement of stimulation electrodes.

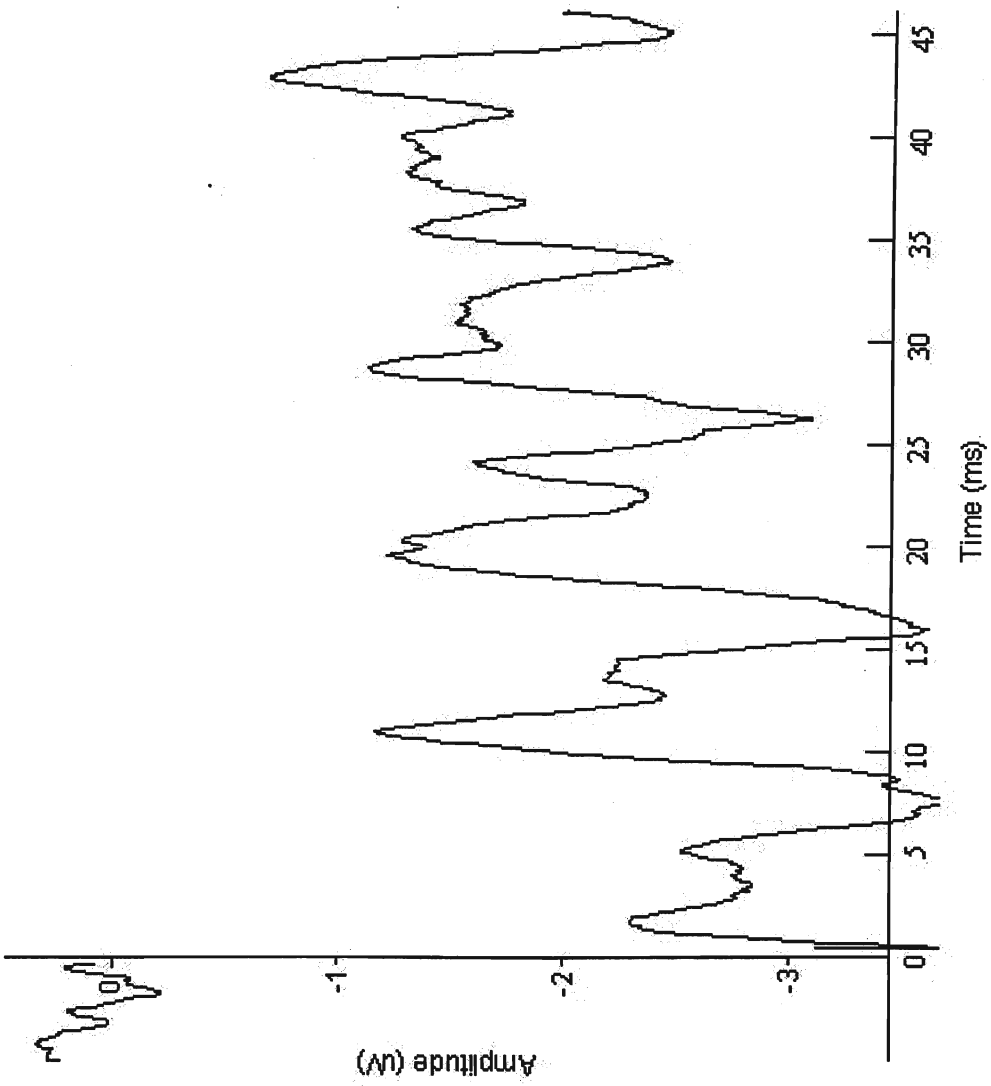


Figure 35.

TSEPs from bipolar lip stimulation - recorded from Ccl scalp location.

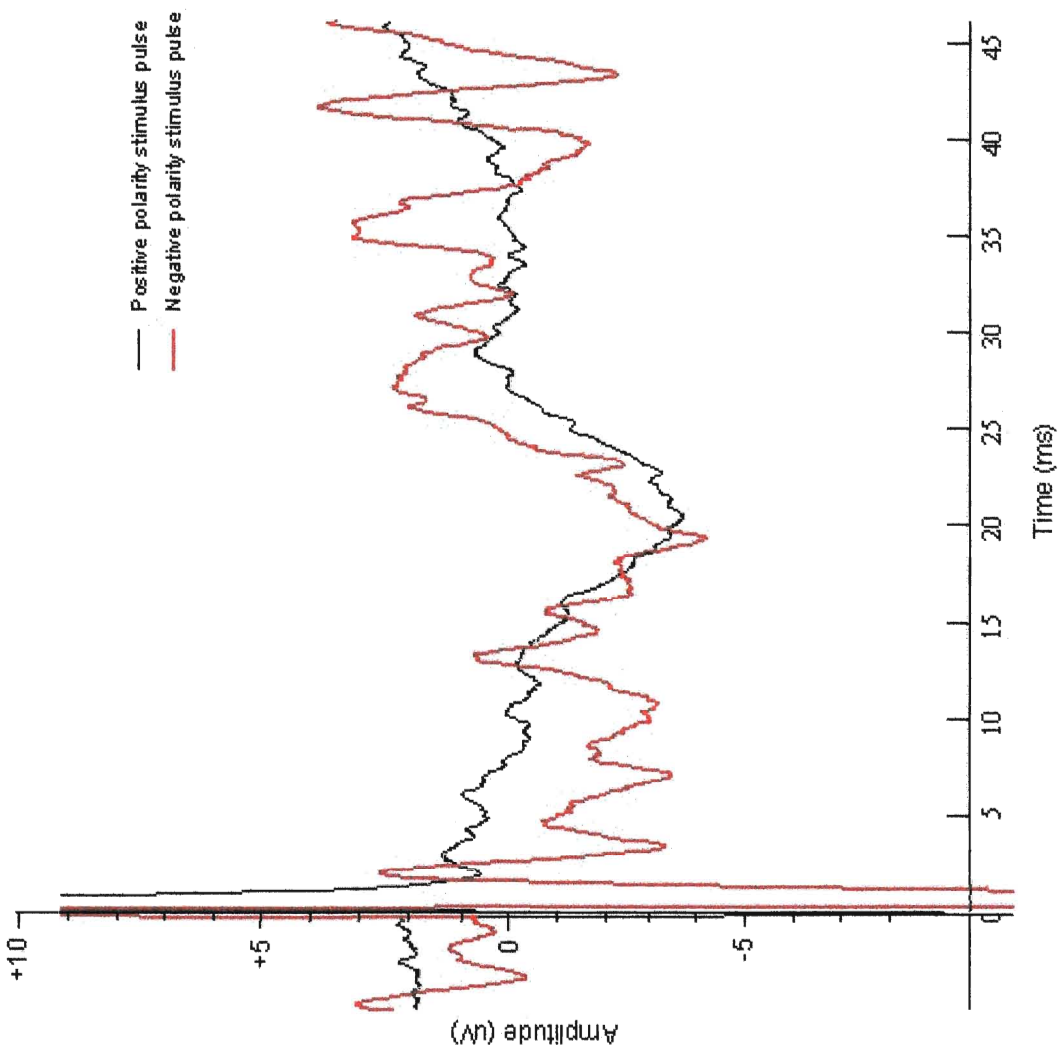


Figure 36.

Average of separate polarity stimulation waveforms in Figure 35.

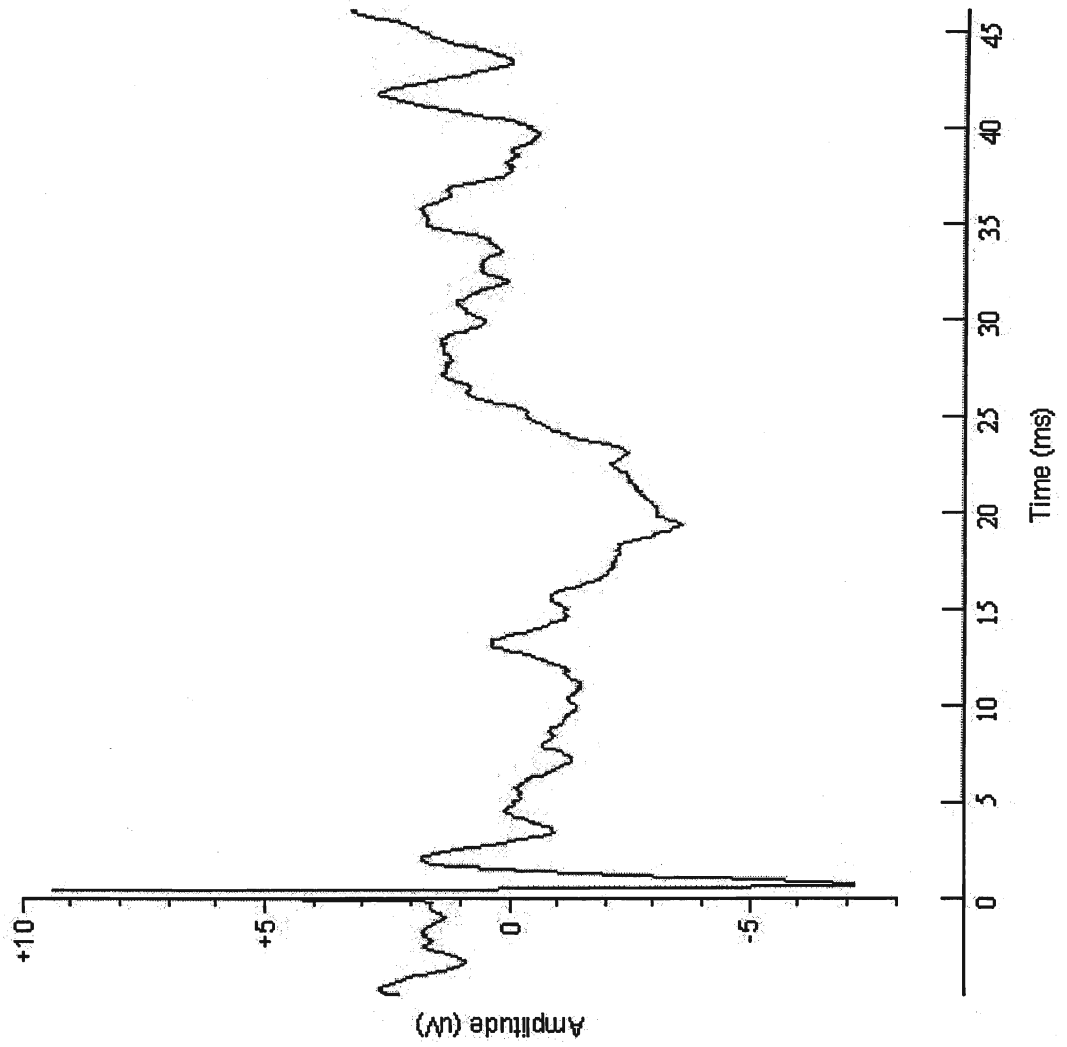


Figure 37.

TSEP from mandibular stimulation at 12 mA stimulus intensity.

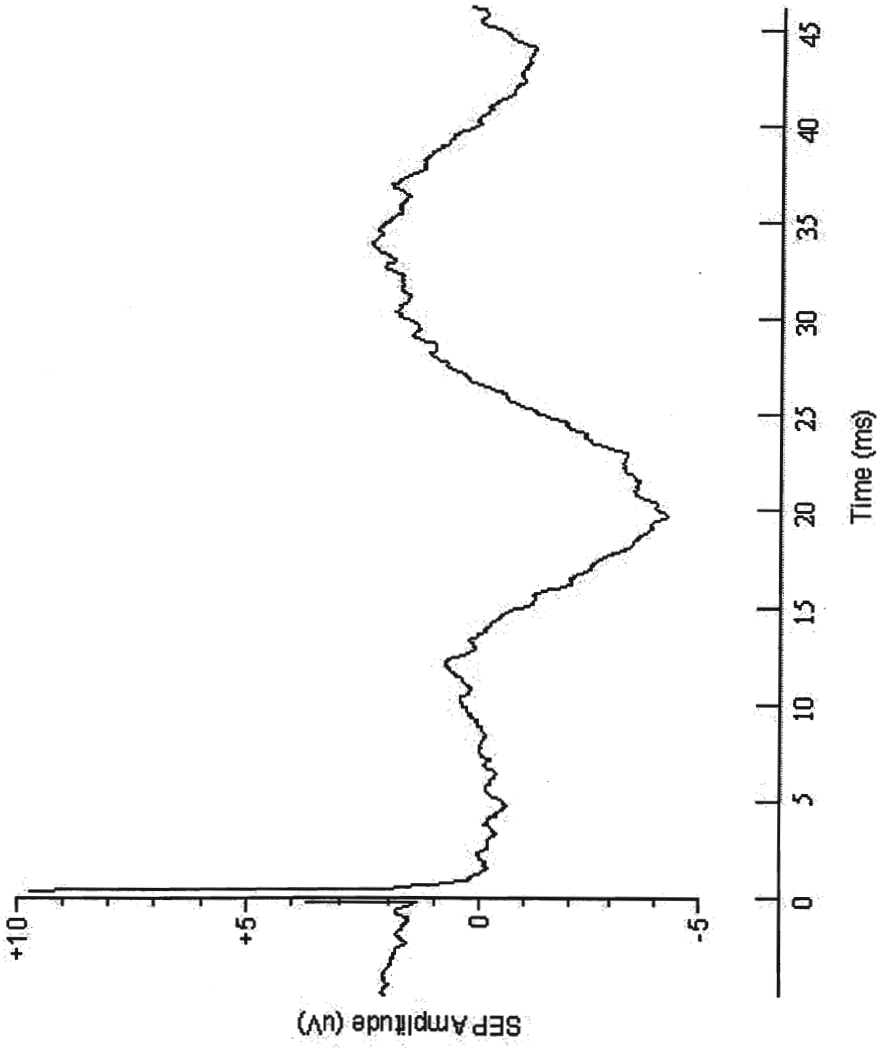


Figure 38.

TSEPs from mandibular stimulation of uninjured participants.

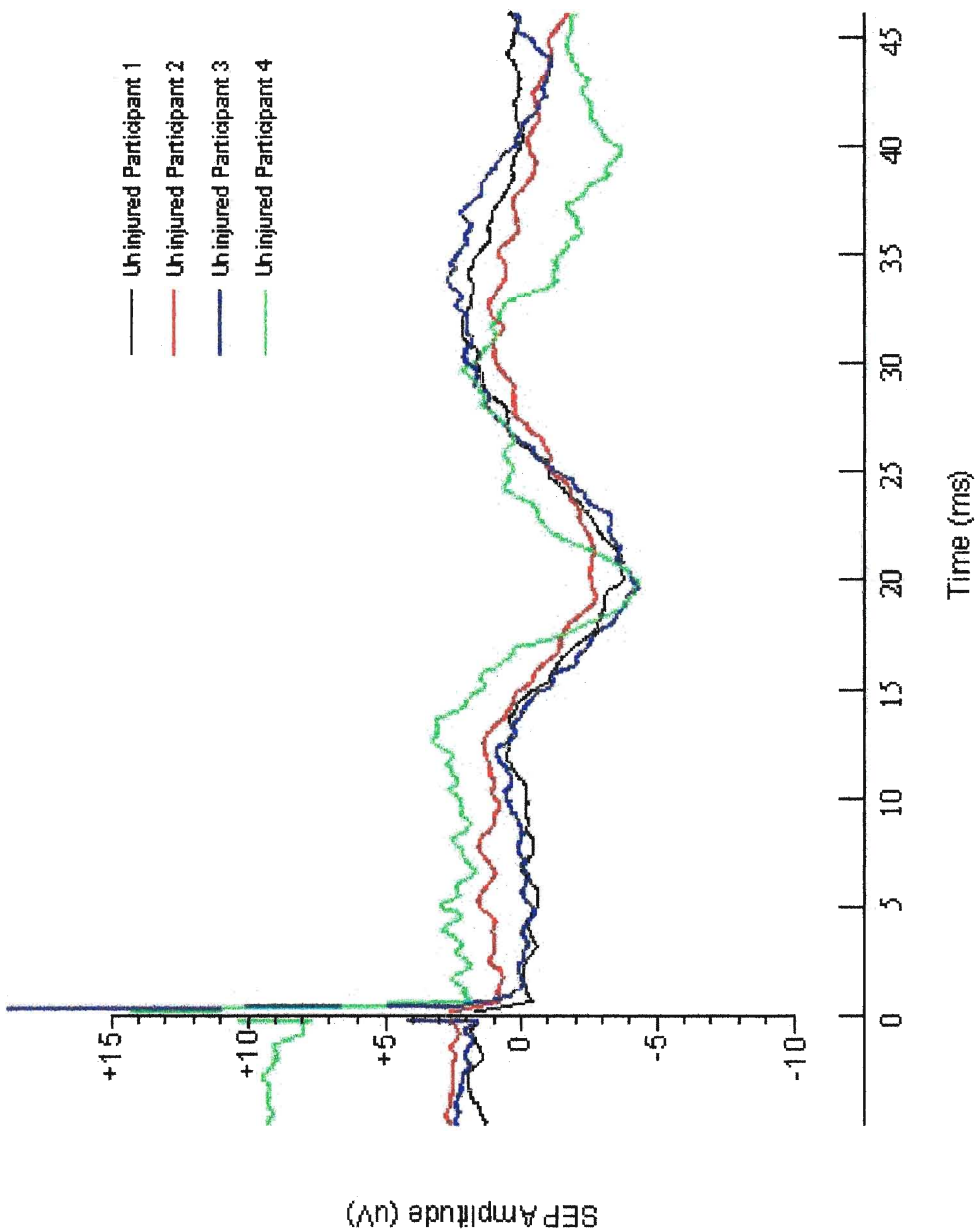


Figure 39.

TSEPs from mandibular stimulation of whiplashed participants.

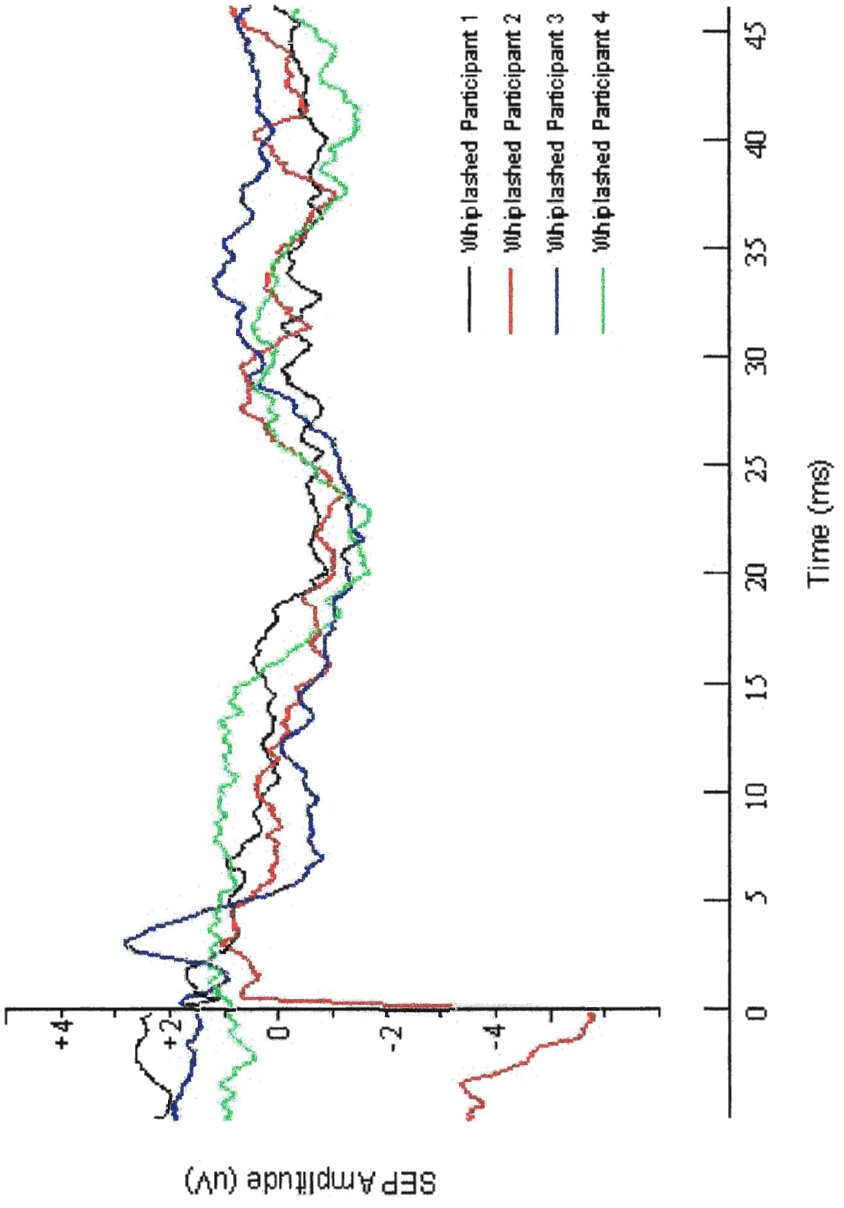


Figure 40.

Superimposed averaged uninjured and averaged whiplashed TSEPs.

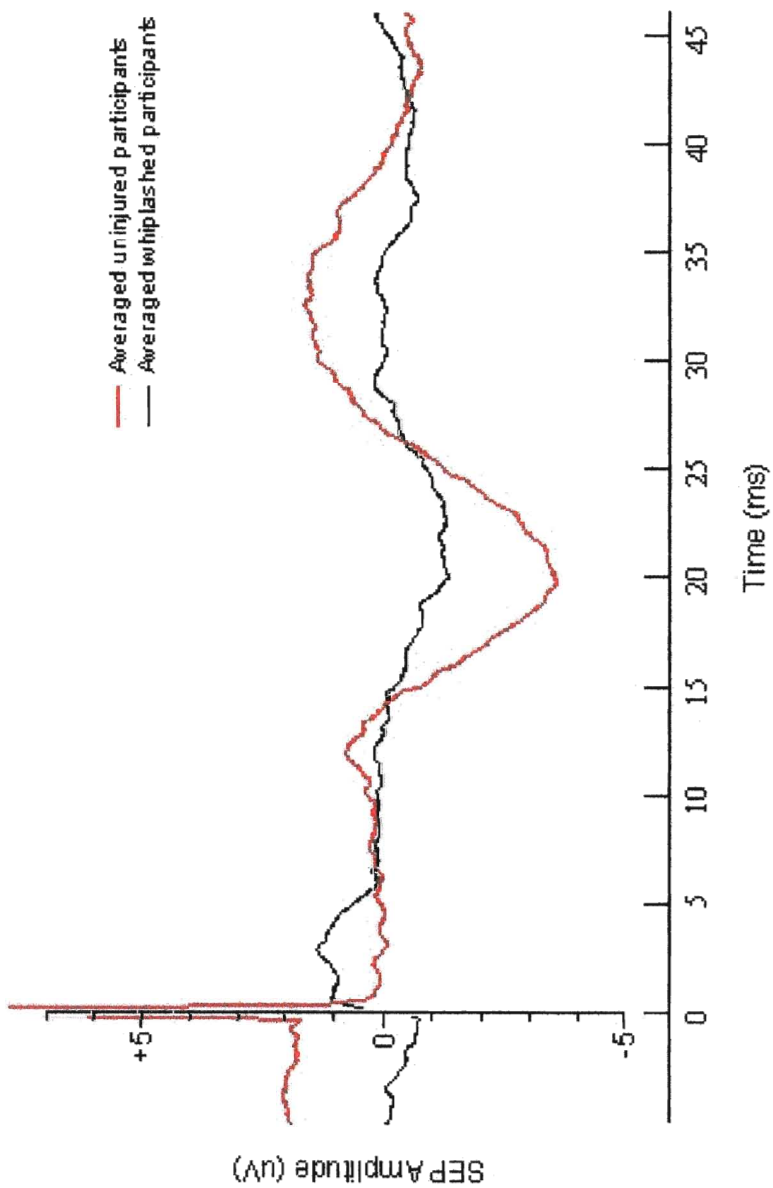


Figure 41.

TSEP from whiplashed participant - 50 μs stimulus pulse width and 100 μs stimulus pulse width.